DB Name	Query	Hit Count	Set Name
USPT, JPAB, EPAB, DWPLTDBD	110 and $111$ and $112$ and $114$ and $117$	11	<u>1.18</u>
USPT.JPAB.EPAB.DWPLTDBD	ampicillin	11779	<u>I.17</u>
USPT.JPAB.EPAB.DWPLTDBD	110 and 111 and 112 and 114	16	<u>I.16</u>
USPT.JPAB.EPAB.DWPI.TDBD	(phenylglycine amide) or (d-phenylglycine amide)	58	1.15
USPT.JPAB.EPAB.DWPLTDBD	(sulfuric acid) or h2so4	186645	1.14
USPT,JPAB,EPAB,DWPI,TDBD	(sufuric acid) or h2so4	30723	<u>L13</u>
USPT,JPAB,EPAB,DWPLTDBD	(d-phenylglycine) or phenylglycine	3390	<u>1.12</u>
USPT.JPAB.EPAB.DWPLTDBD	enzym\$5	176652	1.11
USPT.JPAB.EPAB.DWPI.TDBD	(6-aminopenicillanic acid) or 6-APA	1962	<u>1.10</u>
JPAB.EPAB.DWPI	CN-1165032-\$.did.	0	<u>1.9</u>
JPAB,EPAB,DWPI	jp-05204120-\$.did.	2	<u>L8</u>
JPAB.EPAB.DWPI	jp-02240026-\$.did.	2	<u>1.7</u>
JPAB EPAB DWPI	jp-05204120-\$.did.	2	<u>L6</u>
JPAB.EPAB.DWPI	jp-5204120-\$.did.	0	<u>L5</u>
JPAB.EPAB.DWPI	jp-2240026-\$.did.	0	<u>L4</u>
JPAB,EPAB,DWPI	en-1165032-\$.did.	0	<u>L3</u>
JPAB.EPAB.DWPI	en-1165032-\$.did.	0	<u>L2</u>
JPAB.EPAB.DWPI	cn-1134306-\$.did.	1	<u>I.1</u>

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**Today's Date: 9/1/2000** 

# WEST

## Generate Collection

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Elle: 17181

CITIFE IN TO COME THE PROPERTY AND A PROPERTY OF THE PROPERTY

A nevel App. Milest ester of the seneral formula ###TBl## wherein b.sur.l represents a nyuregen atom, a methyl group or an aryl group, and b.sub.l represents a hydrogen atom or may be taken together with R.sub.l to form a divalent carbon unain residue, or its acid addition salt.

### APPL:

The novel <u>Apply 1.1.0</u> ester or its acid addition salt is prepared by I have independent in a respectation of the sylamino peninillania and F.sub.2 are as defined active, and Mississer of the lamber atom, in reacting a compound of the formula \*\*3000\*\* wherein R.sub.1 and R.sub.2 are as defined above, or its acid addition salt with a corresponding parboxylic acid (VI) or its reactive derivative, (2) thereafter, if required, when the resulting compound has the protected amino group or the group convertible to an amino group, deprotecting the protected aning group to aconverting said convertible group to an amino group, and (3) if curtiber required, converting the product to an acid addition salt.

ine present invention provides also an antibacterial agent comprising the novel <u>Ampioilizh</u> estor and a method for the treatment of infectious disease.

## BRER:

This invention relates to novel <u>Ampibillin</u> esters, processes for their production, and to an antibacterial agent comprising such an <u>Ampibillin</u> ester.

## P.71 P.1

(Mil Tale) of the transplant illing the dised by adylating the emine group of the last to be a sold is a synthetic period in the synthetic period in the synthetic period in the synthetic period in the diseastive transplant, is not sufficient, and this effective in a section of sufficient, and this effects in the synthetic period of sufficient, and this effects in the synthetic period of a section of the synthetic period of the synthet

## 14.71114

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## FATE:

It is an object of this invention to provide noted  $\underline{\operatorname{Arginal_cin}}$  estate a their and addition sales.

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Magnetic scale term tempty to the drop of cracky ambinists are enough Arguminish.

The another as well into inventy has two programs of the <u>Apply in</u> extersion to about the state in pastify and intertinal culties, have fetter exception from the intestinal traws, maintain a high concentration in block over longer periods of time and are less timing than known <u>Apply 1910s</u> exters such as laborated from

### · 19:1

performance of the formula inverse, the formula product of the performance of the contract of the performance of the contract of the contract

## B. 11 B :

A further offers of the countries of the provide a nonexpressing of the cover  $Arg_{ij}(t)$  in each t.

## B : 1 B : 1

Activiting to the aspect, there is terms and advantages are achieved by Argaing and actions of the renetal formula ##ATB4## wherein B.suf.1 represents a nyur den at n, a retny, dring or an argiomrup, and B.suf., represents a nyur den at n, or nyure taken together with B.suf.1 to form a sivalent carring main become, or treir action against a salts.

### POFFE:

Specific examples of preserved Ampivillin esters of general formula (I, are:

### BUFB:

The acid addition salts of these <u>Amricillin</u> esters are, for example, salts of these esters with increaning acids such as hydrochloric acid, hydrokromic acid, hydricdin acid and <u>sulturing acid</u>, or salts of these with organic acids such as contributed and the fact of acids.

## B.11 E :

Invertigations of the present inventors have shown that the <u>Appliciting esters</u> or the activation paralle there is have very desirable properties as quadrate stically.

## ECER:

Figure 1.11, in the laboratories, the  $f_{0}$  policies esters of the invention are easily accurate from the district transformed  $f_{0}$  being a limit  $f_{0}$  in the first transformed  $f_{0}$  being a limit  $f_{0}$  and  $f_{0}$  being a limit  $f_{0}$  and  $f_{0}$  being  $f_{0}$  being  $f_{0}$  being  $f_{0}$  and  $f_{0}$  being  $f_$ 

## 1. 1. 1.

For example, theory almosts after yiel administration in mise, <u>Amplicullin</u> emothy. He will, real without 4-yl mothyl ester nymbouldride and <u>Amplicul</u>, in e.g., e.g.,

## 0 10 1

The investment as a surface of the Weight of the Argenties of this invention is as a content of the first office of the Argentian extends the filty of the property of the first office of the property of the first of the first office office office

## B.11 B :

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ne restrat el ar .

### × . . . . .

In it as to both at the Applicating extends to the Invention base is wit will enty.

## POPP:

Experiments I to i are described wells for demonstrating these advantages of the Angelogy, within the interpretation.

The first open as was raily imministers the active of the plant of the first open as the an until we apply about the experimental animals periodically, and the consentration of Applying in the security was measured by a bicassay method. The blood Applying level ratio was relocated by a bicassay method. The blood Applying level ratio was relocated for no the following equation. \*\*F.\*\*

## E 3 P E :

The results given in Table 1 clearly show that the compounds of the invention show a high body  $\frac{Argio][[[[n]]]}{Argio][[[[n]]]}$  level over a longer period of time than the known [[[n]]] and [[[n]]]

## 1831:

Frodrugs such as Americallin bivalovlokumethyl ester or Ampicillin phthaligyl ester have been known as orally administrable Ampicillin. The ester group of the Ampicillin ester of the invention (i.e., 2-oxo-1,3-dioxolen-4-yl)methyl group) is shown by a formula below in comparison with those of the known prodrugs.

### 3075:

It is clear therefore that the ester group of the <u>Ampicillin</u> ester of the invention pite differs from those of the known <u>Ampicillin</u> esters. It is surprising that the <u>Ampicillin</u> esters of the present invention have the attressid excellent properties as pharmaceuticals over these known <u>Ampicillin</u> esters.

## B3P5:

According to one process of the invention, the Ampicullin ester or its abid addition salt of the invention can be produced by reacting a compound of the general formula \*\*STR6\*\*\* wherein A represents a protected amino group or a group convertible to an amino group, or its salt at the carboxyl group with a compound of the general formula \*\*STR6\*\*\* wherein B.sub.l and R.sub.l are as defined above, and K represents a halopen atom, and if required, when the resulting compound has the protected aming group or the group convertible to an amino group, will make and the protecting group iron the protected amino to up it a newfield about the group convertible to be up it a newfield of the protection of the group and it is a that the protection of the group of the group of the group of the group that it is the protection of the group of the group

## 2322

A compound corresponding to deneral formula (II) in which A is a free amina organization and readily available corresponding.

## -

Are simply, the rope and in probable rouls all can be preferred to converting the tree among aroup of  $\frac{Amperillin}{A}$  to the group A jin this case, the group A is beginghly a protected among group.

## BBBR:

The compound of momenal formula (II) can also be produced by reacting examinization for the carboxyl group with a carboxylic sold of the firstly ##UTF11## wherein A is as defined hereinaboxe, or its same with a carbox with a group with a carboxylic sold of the firstly with a group with a carbox with a carbox

ong unit i i ing mula dili di dambirdaka, i nekarguk, di Mula Batu Mul Kulon 14.

Inter, the Application Wester it general tribular I for its activations all factors. The activated salt is prepared by reacting the Application ester having a free among proup of general formular I with an actid, for example, an inorganity activation as hyperchically actid, hypercally activated and activation activation.

### H.31 H:

Assistants of preferred end alments of the process of the invention, there are process a process for producing the Applicable ester of general formula. I note a contract the whole Acts a deficit case or up of an engine or up with the the charmes of special instance of the process of the process of the process of the process of the acts of up, and thereafter it regards, a newstring the process for producing a mineral acid salt (e.g., hydroshloride, or the Application ester of general formula (II) in which A is an amine group in the form of a mineral acid such as hydrochloride, with the compound of general formula (III).

### - :

Assirating to another process provided by the invention, the Amglicillin ester of general formula I, or its acid addition salt can be produced by reacting a compound of general formula ##STR13## wherein R.sub.1 and R.sub.2 are as defined above, or its acid addition salt, with a carboxylic acid of the general formula ##STR14## wherein A is as defined above, or its reactive derivative at the carboxyl group; thereafter, if required, when the resulting compound has the protected amino group or the group convertible to an amino aroup, eliminating the protective group from the protected amino group, or invertible sality assists a processible aroup as an amino group, and if further required, and other in the content of an acid addition salt thereof.

## 10111

The compound of general formula  $\langle V \rangle$  can be produced by reacting e-m.normalisillaris asid or its salt at the carbonyl group with the compound of general formula  $\langle III \rangle$ ; or by reacting  $\epsilon$ -protected aminopenical anic acid or its salt at the carbonyl group with the compound of general formula  $\langle III \rangle$  and then converting the protected amine armsp of the reaction product is an amina  $\langle III \rangle$ .

## B.114:

The former can be performed presentily by reacting chamin penintilianing and or its salt at the parfoxyl group with an equimplan amount, or a molar excess, of the oppound of peneral stroubant. It is an inert craaning solvent such as tetranyoroturan, didxane or abetone in the opticial presence of a base twick deaminopenicilianing acid is used, the presence of a base is preferred at a temperature of from about 1. degree. 2. to room temperature.

## 11377

The larger can be performed preferably by reacting depicted and periodism of the animal proup at the e-position protected as the e-position protected as a solution against the sample and the e-position protected as a solution associated as a solution as a solution as a periodism protected as a solution as a periodism periodism as a solution as a complete e-phenylapetylaming and illamic asia is benegligable in the tirst-remained process, thereafter reaction the resulting e-protected aminogenical land asia as as with phesphorus pentachloruse and a lower alocked such as methanic at the temperature of the periodism e-protected aminogenical land as as a temperature of the pentachloruse and a lower alocked such as methanic at the temperature of the process of the past of the such as methanic at the temperature of the process of the past of the same as the results of the same and the results and the results of the same and the results of the same at the same and the same and the results of the same at the same at the same and the same at the

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### ....

The reaction returned the original to beheral formina. Which its activation is also the data by a solution denoted in the Mill of its reactive serious original to beheral formina. IV. When the original is formed in the first appropriate to an aminomity, the protection group is removed into the protected aminomyroup, or the converted group is converted to an aminomyroup and if desired, the protected converted to an aminomyroup and if desired, the protected converted to its activation salt. Thus, the Amplitude esternic general converted to its activation salt.

### 1. 1.

And restoring the presence of the appropriate of the above processes, there are provided a processed of processes of the action of the resulting the Schiff base group or the commune group TAT of the resulting compound to an amine group and if required, converting the product into its actional adultion salt; and a process for producing an acid addition salt, such as a hydrochloride, of the Ampiculain ester of general formula IT which comprises reacting a compound of general formula TTT in which A is in the form of an acid addition salt such as a hydrochloride with the formula of general formula TTT.

## . . . . .

After the reaction, the  $\underline{Appinillin}$  if general formula. It or its acid addition salt can be istlated at hyperfied in a systematy mapper.

### ESER:

The <u>Ampivillin</u> ester of general formula (I) or its pharmaceutically acceptable acid addition salt is converted back to <u>Ampivillin</u> in vivo when administered to an animal. Accordingly, this invention also provides an antibacterial agent comprising the <u>Ampivillin</u> ester of general formula (I) or its pharmaceutically acceptable acid addition salt as an active ingredient.

## F. YE F:

The antibacterial agent of this invention may consist only of the <u>Ampicillin</u> aster of general formula [1] or its pharmaceutically acceptable acid addition salt, or a mixture of it with a pharmaceutically acceptable carrier.

## BSFR:

The pharmaceutically acceptable carrier may be those Jarriers which can be used in formulation Ampicullin. Examples are starch, lactose, hydroxypropylogicalline, religious, massagnate, and calcium stearate.

## : : : :

The antibactural spant of this invention is administered to man and other animals in a free of  $1 + 5 \approx 0$  ma by body weight by calculated as the  $\cos t \cdot \cos t = 1 + 1 \approx 0$ . Is plantaged to all plants as the  $\cos t \cdot \cos t = 1 + 1 \approx 0$ .

## 3327

Ampirillon femethylelerarel, Redirarlenedeyl menhyl eshem (Rusubul enethyl) Busubul obym ren ,

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## H.3377:

Argunillin .- exc-rephonyl-1,3-dioxolen-4-yl/methyl ester E.sub.l ophenyl, E.sub.l =hydrogen ,

## 4.11

Amplication ..., Ferral myllic wy-decyclonewen-leyl ester Russial and Busubul, Forther transfer on the or the efficiency element for an amplication of the state of the state

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H. H. .

A. Approximate formethy:-2-oxe-1,3-dioxelen-4-yl detnyl ester hydrochloride compounds of the invention

1. 17.11

Fig. Animals of well-paragraph, that we consider the rays estimated as a substance of the convention.

is  $\frac{de_{1}}{de_{2}}$  in the larger particular of the constraint where the constraint where for the first  $E_{1}$  and  $E_{2}$  is  $E_{3}$ .

F.31 ::

i. <u>Aprili Zin</u> trinye itwo wata i

TABLE 1

Line Live I save ratio

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Line Line Live I save billing billi

The invent. N.B...4 L.F.2.4 1.7 [12] 11. Known Tompound C 3.3 1.8 1.4 1.1 1.9 2.4 Control compound C 1.1 1.9 1.4 1.1 1.9

BSTL:

Ester group

Ampicillin pivalcyloxy methyl ester

##STR5## Ampicillin phthalidyl ester ##STR6## Ampicillin ester of the
invention ##CTRU##

11:11:

Amplication of this process of the mag was dispersed in 6 ml of dimethyl formamide, and lut of at procession hydrogen perhaps was added. The mixture was cooled to life the lateral strong behaved the first was added, and the mixture was strong at 'language. On for life hours. Then, life mg of potassium hydrogen carbonate and 32% mg of 4-bromomethyl-8-phenyl-1,3-dioxolen-2-one were added, and the mixture was further stirred at 2.degree. On for 3 hours.

Water 1 mil was assed, and the mixture was concentrated under reduced pressure to distrib our aperturing. The apertus layer was repeatedly washed with ethy, aberate, and saturated with scalum chloride. The separated oily substance was extracted with 50 ml of methylene chloride, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium subtant. The dried craumic layer and concentrated until the amount of methylene chloride decreased to one half. Isopropyl algohol 130 ml/ was added, and the mixture was again concentrated under reduced pressure to give a solorless solid. The solid was collected by filtration, and washed subjectly with isopropyl alcohol and ether to give 320 mg (yield 46.4) of [principle 1 = x = 1 = x

- 1 1 h

The resulting  $\frac{Approx.lin}{a}$  ester hydrochloride was incurated in 40 mouse block on pH 0.4 phosphate buffer at 30.degree. 3. for 10 minutes, and then subjected to block organization. It was found to be completely converted to  $\frac{Amprox.llin}{a}$ .

THEF:

we take thing mater that was abstract in early introduct in the result. In the control of the co

rd of 4-re roberthy. - -rethyl-1, red. x lenel- newere added, and the rixtime was observed at the dreed. The form wise Aiter the feathing the reaction rows of the water. The protection of the way extracted with the control of the control of a very was many points. The water three protections of the control of the contro tures, and dried the ampurius radies in stitute. The enny aretate was mentiled off union require pressure to give a yellow syrup. The resulting syrupy residue was dissolved in 4 ml of a monotonia and the solution was aboustwart: pH L., with driving nydrichling acrd. The silition was then stored at the dreet. I self-computer. Water I fill was asset, and the and buttour was postuled to disper entried pressure. The against layer was design to repeate toly with entry, a setate, and then get tranea with side, in this in terincomparated by detaile was extracted with the first pethylene on it. As, and was new form a standard agencylene of the first pethylene of our first was drived over annymble was dismostly to its polimer and outselves and outsentrated under request pressure to the half it its volume. It the solution isopropyl albohol .30 ml was added, and the mixture was again concentrated under reduced pressure to give a colorless anorphous solid.

## DEFE:

The solid was collected by filtration and washed with isopropyl alochol and when to dive 31, but yould 82.6 of <u>Ampiotition</u> enough a solution was a collected

wrogo well in The project naither is wing properties.

The resulting  $\frac{\text{Anni-Miles}}{\text{Constant}}$  ester hydrophloride was incubated in 41- mouse blood of resulting  $\frac{\text{Anni-Miles}}{\text{Constant}}$  of for 30 minutes, and then subjected in pH 7.4 phosphate buffer at 37.degree. C. for 10 minutes, and then subjected to bicautography. It was found to be completely converted to Ampicillin.

By the game means was shown in Example 1,  $\{2\}$  , lifting of Ampirillin ., je redovnyl Howyele by Cohemenyl Sester by in phlyride was obtained as a njiroess afirmo ka solid maro kapom <u>Arminijion</u> tribydrate aba 1 a m r-ğı bu-i,.-hark nylangxynyninnexede Tylelduk ... ...

## DEFR:

The resulting Ampibillin ester hydrophloride was incubated in 40% mouse blood in pH 0.4 phosphate buffer at 37 degree. C. for 10 minutes, and then subjected to bicautography. It was found to be completely converted to Ampibillin.

## 

And the property of the second was dispersed in 40 ml or dimethyl formanide, and the relative tassion by it can be whenever was acted. The mixture was explaint . Washer. The mixture was stimed at Landon to the mixture was stimed at Landon to 6.84 are-. The control of the mixture were added 500 mg of proassium hydrogen rarbonate and 1 g of 4-bromomethyl-1,3-dioxolen-2-one, and the rimited was stored at the research to desire a. It is not by hims.

## CHIR:

Marer [] nl was aided, and the mixture was undertrated under reduced pressure to remove abed not be. The appears layer was repeatedly washed with erby) aberate, and sar mared with sodom biliniae to precipitate an orange aurėliko symstanos. The apiscus layor was norived by detantation. The sum-like sukotanos was auto luos in rotnanti, iki slimino kwiji augustėj tarbon, syslej to the next the analysis into the really stimed other to precipitate a pare branch solit. The solitiway onlike diby filtration, and washed with a rixture of ether and methanol to give et ma great de for <u>Ampholitic</u> l-oxo-l,3-dioxolon-4-yl\methyl ester nydrochloride as a pale orange amoryhous salii.

## PEFF:

The resulting <u>Amphylling</u> ester nyir dil ride was in thated in 4 corder il a corde following the first special or the first section of the first section of

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originally, and the solution of the property was formed. The spheric pentagonality of the property was stirred at lidegree, to the steel. It for a nours. The solid precipitated was collected by filtration, and repeatedly washed with methylene offcride to give 13.1 g. yield 91 of the explosion of the spherical property.

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After the reaction, the still was separated by filtration, and the ribrate was in reducated in the reduced pressure. The reculting syrap was also used in water, and washed with estate. The aquerus layer was saturated with solid modulate, and the separated ally substance was extracted with nethylene to it. The extract was washed with a naturated appears solid in or sodium ablorus and other trated until the amount of methylene chloride decreased to half. Upon addition of isopropyl alcohol, a colorless solid was precipitated. The solid was collected by filtration and washed with isopropyl alcohol and ether to give 132 mg (yield 54\*) of Ampibilian (5-methyl-2-oxo-1,3-dicxolen-4-yl)methyl ester hydrochloride as an amorphous solid.

## 1888:

From . The state resulting ester hydroghlorize and 95 mg of The epochylacy optimization hydrochloride, 140 mg (yield 86 ) of <u>Appiniting</u> . The median optimization of the explosion of the explo

## TEFF:

Five grams of (5-methyl-1-oxo-1,3-dioxolen-4-yl'methyl 6-amin.penicillanare petolygnesulfongre was suspended in 30° ml of ethyl acetane. To the suspension was added at 1.dernee. 1. 11 ml or 4. aqueous solution of sodium nydrogen take have 5 to 6 with 15. The mixture was rigor usly stirred. The ethyl instate layer was sequented, washed with ide water, dried at C.deareg. C. over apply that manuscript sulfits, and consentrated under reduced pressure to give a pale yellow syrup. The syrup was dissolved in 50 ml of methylene chloride. The mixture was stirred at C.degree. C. for 4 hours. After the reaction, the ineclaris paterial was equalated by filtration, and the filtrate was concentrated under reduced pressure. The resulting syrup was dissolved in water and washed with ethyl abetate. The aquebus layer was saturated with sodium offictide. The separated oily substance was extraored with mathylene military, where with a saturated appears solution of sodium chloride and dried two addy in the edition buildate. The dried a lutton was a interpretate in its reals approprie that it has an upit of methylene unitride as meased to the balf. Teaps you act not was abled, and the mixture was abalic shread their inless to sure dipression to size a sufficiency of the solid was as 100 making to start in, and washes with other to give one or yield of the Appropriate employers with their teaps to size any problem to a second with the second with amrightia a lidi

## 1313:

An ernand solution of the cylin kypropyl religious was prepared and added to the <u>language</u> of source hypropil ripe and langue. They were kneaded, extrince the output of a solution of the solution of the solutions.

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 hydrochloride
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                  Froduction of Angles.ion (Esmethyl-L-dwo-1,3-diswolen-4-yl)methyl ester
(1) Ampicullin (5-methyl-2-oxc-1,g-
 dioxolen-4-yl/methyl ester hydrochloride 356.7 mg Lastose 36.3 mg Magnesium
 stearate 8.0 mg 400 mg in total
.l' <u>Ampibillin</u> .5-methyl-l-oxo-1,3-di-
oxoled-4-yl methyl ester hydrochilorde sod. my last se vit.3 mu
hydroxorpyl e ... e ... nad., o nadnot ta.
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prolen-efylprethylpster nyajoonjorde aga ingspallias cellulose illag
 lactose [19.3 mg Hydroxypropyl cellulose 1) mg Magnesium stearate 5 mg 500 mg
 I. An employment of the family a maily of which his while represents a night of a form a market sector of the family of the business of the family of the fa
  main residue, or a pharmaceutically acceptable acid addition salt thereof.
 \epsilon . An antibarterial agent comprising an antibacterially effective about it an
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  what he taken it should be the strong a reptable and a duto it wall there is in
 Per Baryon Marin a pharma e durantly arregulater carriers.
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The Armonda production of the control of the formula ## "[Br]## where,h B.dw.,l represents a hydrogen at m, a methy, go go man any, drog, and B.wwh., represents a hydrogen at m i may be taken to bether with B.ww.l to form a divalent tags homain fewering, or a pharmaceutically acceptable acid audition salt thereof.

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## 8.448

Into invent, a relates to a an improve quivess to preparate as in the factor and an exploration of the garent aming special-capture with an angle  $\mu$  and  $\mu$  agent.

## F. `F F :

Today, semisynthettic theta.-lactam derivatives such as amplyillin, amowing lin, perador, perhalexin, perhalexin, perhalexin, perhalexin, perhalexin, perhalexin, perhalexin, and perhalogly sin are, in an industrial scale, prepared by phemical methods, for example by reacting an amino theta.-lactam such as 6-aminopeniculants abid, usually having its barbawyl group protected, with an activated side chain derivative, followed by the removal of the protecting group by hydrolysis. For example, ampicilling 1-17-alpha.-amin phenylacetamido-penicillanic abid) can be prepared by reaction (1-200), having a suitable protected carbowyl group, with bidding the control of an interpretable of the protection of the prote

## ESTR:

Within the last years, there has been an increasing argunt of publications to certain the posterility of engine to preparation of periodilities and opposite the posterior and the parent area on a transfer of the example, and the parent area of the example of

## 14,111.4

In equipment of a color one of an units of cracellar an with an anylating when may be post in the presence of a soltance and case of anylase whereby the colored detailed and are represented by the colored detailed and derivative date the same upstacellar an intribute. In the cretacellar and post-various empty down the e-MH.s incomes the representation of the pener parent clertacellar and to the C-MH.s incomes the charm of the representation to the representation of the representation to the representation to the representation of the representa

## h. 1 - :

In this process, a periodic fractions, at these conditions that are the continuous of the reaction, and increased on the following the reactions of the periodic of the decomposition of the liberation of the action of the act

i demperator, at coment two constants is descriptively in pay take places around being as reaction.

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It has now, surprisingly, been found that improved process conditions are claimed if the <a href="https://www.nic.gov/patro">https://www.nic.gov/patro</a> explaints of the amine obstacle of performed at the text of the parent union obstacle area and the trivial name of the parent of the obstacle of the text of the parent of the obstacle of the text of the obstacle of the text of the obstacle of the text of the early area of the early area of the first of the gardent amin, seets, the tax of the saturated concentration of the dirrespinding applicing agent.

### 1 41 5

The spetau-lastam Herivative formed may precipitate during the reaction and, as , the abid form of the adulating agent such as 1-phenylglycine and 1-phonyl dayline may precipitate. Hence, in some bases the reaction costure will be a substitution of the feature.

## 12.1.1

The [parent amino .beta:-lastam has a free amino group which is adylated by the reaction apportion; to this invention. The amino .beta.-lastam may conveniently be <a href="https://example.com/reaction/beta.-lastam">https://example.com/reaction/beta.-lastam may</a>

## DEPR:

The amino Aleta.-lastam, for example 6-AFA or T-ADDA, used in the process of this invention may be obtained by encymatic hydrolysis of the fermented penincillins or dephalosporums, for example penincillin V, penicillin C or dephalosporum 2 or their ring enlarged analogues (for example V-DCA and 3-DCA or derivatives thereof followed by removal of the hydrolysis by-product, if desired phenoxyacetic acid etc.). Advantageously, the crude solution can be used directly without further purification or dilution.

## DEFR:

The adylating agent may be in an activated form. Preferably, the adylating agent is an amide or an ester. The adylating agent may be a derivative of <a href="T-thenyl plycine">T-thenyl plycine</a>. The hydroxyphenyl plycine, D-2, E-dihydrophenyl glycine or manually addition as a lower alkyl ester (methyl, ethyl, n-propyl or left propyl ester) or an active which is unsubstituted in the roll of the advisor of a salt, for example, the nyme of the advisor of the H. substitute form may be rounded in situ.

## TEFR:

The solubility of the adylating agent such as the T-ghonylglycing or 1-p-hydroxyphedyldlycine derivative will vary with the identity of the Schwick add with the composition of the reaction medium. In an aqueous event as use in the exceptes, the solubility of the hydroxiloride salt of the hydroxiloride is typically approximately 400 mM. However, the solubility is our, dependent on the salt components in the solution, as well as on the pH value and the temperature of the solution. As a further example, the solubility of the sulphate form of T-phenylglycin amide is about 3.3 M within a pH range from 0.5 to 6.5.

# DF18:

Framples of .but a. -lactam derivatives that may be prepared by the process of this inventor are appropriate, amonifility, refacior, dephalexis, replainment, opportunity, opportunity, appropriate, epocifical and obtained in

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The <u>charge</u> to be seen income process of this invention may be any <u>encyment of the processor</u> and the respect of the present of the second o

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The stituble pH value depends, inter alia, on the type of the enhume used. Using Particular This could thruste, the pH value is typically in the range from  $\ell$  to  $\ell$ , preferably in the range from  $\ell$ . For the preparation of am widiling a fill value in the range from 1.5 to e.4 is preferred. Control of The FH Value Kaplan aged.

### - F - F :

Sultable encyre on entrations have be from 1 to 1 % T/ml of To he unit of enaying an ivity, see helpst.

Third the pit two are rither to this invention, an extrapromary high metarat. Detween the arthur or skotaselantar derivative which can be restrered and the total arount of about the completion agent and be brained. Installifus participate outsiness twing the teachings of this importing and graperly relecting the concentration of the anylating agent, the ratio between the concentration of any ating agent and the starting ability includes a -lighter, the pH value and the shryme. Thus, a ratio of 2.4 was obtained in Frample 1 below mount the process and plant to the present invention. In a comparative batch promase, vide Example 1 felow, a molar ratio or whily 1.4 was fittained. In addition, the yields of isolated product obtained in this example were lpha and er , respectively.

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As a popular some transminent of a system of the contrast of t to Furgish patent Luch, is applied.

As a principle is possible, in A anyloge antivity the roll wing is used the short of principles roughly as a small of engine that hydrolyces per minimal 1 . Which is pure visiting a small 2 make at an array of fitting 1 or 2 its 2 results 3 or 4 and 4 respectively. The value 4 of 4 respectively.

The equipment for this experiment pursisted of see FIG. 1 a thermistated resource having a pulse of 1.5 laters, equipped with a three-fielded injector and a sleep with sold lessons per area after the The readily was consected to an autotitization system using 4 M subjects and 6s totale. A valve was positioned at the outlet of the reactor. The outlet of the valve was connected via a pump to a pasket centrifuge equipped with a polypropylene may having a density of 1-b union. The outlet from the centrifuge was dense Med via a pump to a feed mank equipped with a stirrer and a glass sinter notion. The outlet from the seed tank was connected via a pump to the reactor.

### 1 8 8 8 :

A mixture is more that it is in the reason with the first value closed. The stirring was started. Immobilized Penicillon B anylase (attach Value was maintained at  $\theta$ .). The reaction temperature was about 20 degree. C. Under these conditions, the reaction mixture was almost saturated with D-HFGM and  $\theta$ -AFA. Then, the bottom value was opened allowing the reaction mixture from the reaction to enter the centrifuge. Thereafter, the mother liquor from the reaction to enter the centrifuge. Thereafter, the mother liquor from the reaction  $\theta$ -AFA  $\theta$ -1. The purpose into the feed tank wherein D-HFGM (21.7 g, 120 mmol) and  $\theta$ -AFA  $\theta$ -1. The purpose is about To mi. A flow of about 100 ml/min was maintained in the system. The concentration of reaction components in the reactor, in the reactor outlet, in the centrifuge outlet, in the feed tank and in the feed tank outlet were monitored by analytical HFLC.

## CEFR:

As the reaction proceeded, the amoxicillin and D-HPG formed started to precipitate out of solution. The crystals were separated from the immobilized company antibles by the bottom sleve in the reactor and the crystal suspension was lost of the solution where the opportule were separated from the mother of the country of the solution of the country of the solid D-Hi Wald of the solid solutions of the solid solutions at the saturated D-HP Mand of the total contentrations of D-HP Mand of the saturated D-HP Mand of the total contentrations of D-HP Mand of the saturated by the solid substrate was added to the feed tank. At intervals the crystals in the centrifuje were washed with water, the washing liquid was added to the reactor. The amount of water used was sufficient to keep the volume in the reactor at its starting the lights.

## . . . . .

After about 11 hours, the desiry of D-HFOM and e-AFA was stopped. After 14 hours, the e-AFA concentration reacted 10 mM and the reaction was stopped. The arounts of reaction components are given in Table 1, below.

## 

4 of 6

A comparative experiment was performed at batchwise conditions and the continuous stopped at the popular where the optimum yield of emoxicillin was accurated to notes. The relation temperature was about 17 degree. I., the pilot, the was about 17 degree. In this example above, was used. The total volume of the reaction mixture was 1 liter. The court is was part inclination result in particular above. After 1 hours the court of value was performed, and the object as were separated into the immutities example above particles by the continuous sleep in the result. The divisual suspension was filtered. The amounts of reaction components are given in Table 1, heldw.

A mixture singularity of D-HEGA (1),  $\gamma_{s}$  (1) much and  $\epsilon_{s}$ -ALA in  $\epsilon_{s}$  on water, which was adjusted at a pH value of All by adding 4 M ammonium hydroxide, was audel of the ready with the butting valve bigsed. The stirring was started. The minimum of the control of the co temperature was as it is a trace with 1-HF WA and <u>TTAIA</u>. Then the soften valve was paneled as the season of earliest with 1-HF WA and <u>TTAIA</u>. Then the soften valve was paneled to the soften the sential median arter, the soften light of soften the sential was paneled into the feet that were liaded. The total volume of the suspension in the feed tank was dept at about 15 ml. A flow if about 10 ml min was raintained in the system. The streamtration of reaction sumplicants in the seasons, in the reaction spilot, in the sential decorate of the sum of the sum of the sum of the seasons. s sifteen fly analytics. HFI 1.

The orystals firmer in the reactor were separated from the insubulized capping particles by the bottom sieve in the reactor. The crystal suspension was 14ato the sentrifuge where the crystals were separated from the mother liquor. The mother liquor was passed through the feed tank. When the total concentrations in the feed tank came down to about 180 mM HPGA and 225 mM E-APA, more solid was added to the feed tank. At intervals the crystals in the partrifuge were washed with water, the washing liquid was added to the reactor. The amount of water used was sufficient to keep the volume in the reactor at its starting level. After washing the prystals in the centrifuge, the vents: ige was errited.

## 

After about 12 hours, the desing of  $\frac{e-AFA}{e}$  to the feed tank was stopped while the D-HFGA desing was maintained in order to keep D-HPGA at saturation. After 14 hours, the  $\sqrt{6- ilde{A}^2A}$  consentration reached 20 mM and the reaction was stopped. The amounts of reaction components are given in Table 3, below.

## 1.551:

## 1815:

HELD Analysis of Ampunillin and Caphelemin

Encymatic Preparation of Amoxicillin from D-HPSM and n-APA

Sport of the Brog as at the of American line from CHECAA and 15AAA

Bergain indin Longs (in dichines: 4.1 | 17-13 ; 6.3 | 7-ADDA ; 6.1 | <u>6-A</u>GA ; 7-11 | 17-138 ; 13.4 | Dephalomin ; 13.8 | Anglinil<u>lid</u>; 13 (0-13M).

Retention times in minutes: 1.9 Dep-hydroxyphenylalycine; 7.8 DeHFGM ; 3.1 rempary 5.4 <u>seata</u> / 4.4 Ambrich Tib.

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NITER-POSTIMENTS:ER 440844; ER 44089; ; TS 4170840 ; A. HULLON, ; A. HULLON,

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ABSTRACTED-FUB-NO: EF 012443B BASIC-ABSTRACT:

Profit of a beta-largam merit. is plained in which a beta-lastam nucleus is a great to large year to an include in an enough to reaction, and the encyme, a limit large year to a serie out. After the encyments reaction, the Srti. mixt. "from which at least the encyme and solid 1-theory, your hadreness of menoused, is treated with an aldehyde at a pH of 1.5-e.) and the Schiff base of M-phony, glycine amide is sept. out.

YME - The coupling reaction is used for prepriof important antibiotics, including ampicillin, rephalemin and Setaclor, in which the Beta-last of hydroare respectively of montrolloid and taken to the Al-A-, "-aminodesa terms y-opening transfer in the Al-A-, and related puls.

AnyAnyAugh - The 1-quencyalyring amide derive is easily sepa, out in pure form, preference the beta-lastam prod as the solubility of the latter is nigher; recovery and purificn of this prod by known methods, is simplified. Recovery and recycle of the 1-phenylylyzine amide derive is by simple filtration or extra, it particulates altehyde bencalathyde is used, excess aldehyde takens as extra solvent, although other solvents, or mixts with PhOHO, can be used. The school base is then split with sold, as Hook, and recycled. As an excess dramatic is issentiable toupling to obtain a high yield it beta-last at the research the coupling to obtain a high yield it beta-last at the research to provide a temperalally according to the set; of the relation mixt typically contains 1-7 moles of the high hydrogeneous and the last and the last

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## 3-174:

Timerous methods for the synthesis of penicillins or sephalosporins have been which is a the literature. The major part of these syntheses involves the reaction of  $\frac{6-4m_{\rm eff}}{1000}$  per of the portespinding Frankhovephen compounds with an a mivated derivative of the acid, with which the amino group is to be amylated.

In one aspect of the invention there is provided a novel intermediate for the synthesis of derivatives of 6-ABA or 7-aminocephem compounds in high yields.

The stricture of the rong sun is having a multi-like keen established in the coast of their like and LLMS spectra + LLMS. The spin-spin suppling pattern of the latter shows that the +.alpha.-hydrogen of the C-amino ephem derivative is strongly surpose conding [Lalpha.-hydrogen of the C-amino ephem derivative is strongly analysed we help the introduction of the phosphorous atom.

in -APA derivatives with a free NH.sub.2 -group the proton in the  $\epsilon$ -p sitlen for namely seen as a imblet at .d-lta.v4.4 - 4.8 ppm - N°1.sub.5. However, as an example in a p-APA tribute the facility to a implicit. Example 1, talk proton is named as a material consistence of peaks in the region at .welfact 4.8 - 1.1 ppm - N°1.sub.5, proton which by first order analysis the following action and the complimation of the contract of

It is even more surprising that a compound having the formula  ${
m I}$  , wherein  ${
m R}$  is a secondary ammonium group can be reacted with a haloghosphite compound to form the Sorresponding phosphiteamide compound. However, it has been found That for emapple (-aringenial) and aring or T-aminodesa with systephalosystams of arms, when independent is a controlled to this form in the presented of two courses of the system of t to par a main visua tak alethylarithism kalt (p k-knylenga splottarit spanitillanit asid or

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Among other activated acid derivatives which have been used in the acylation of the amino group of e-AlA or derivatives thereof are various forms by a covariant esters, which performs hence, by an instruction esters and the like.

## 231F:

Few syncheses of year fillin or copholograph derivatives are known in which a free parboxylic apid is reacted with a derivative of  $extsf{C-APA}$  or a 7-aminocephem empeted.

The specification of British Patent No. 1.268.836 disploses that 6-isobyanato positification arise may be prepared by reacting phospete with a  $\frac{6-AFA}{6}$  ester. The (-isomyanato penicillania ester may then be reacted with a free acid to yield a penicillin agriculture. However, this rountion can only be performed with moderate yield, and furthermore this known synthesis is not fully andertable because of the use of phasgene which is poisonous and technically alirianis ta bandlé.

## FREE:

The above reaction can be illustrated by the following reaction scheme, in which a c-AFA derivative of the formula I is reacted with a carrowylic acid: ##STRe## in which B has the meaning defined above, and R.sup.3 is an organic mount.

## Harris:

In a contribut empodiment of the method of the invention phthalide esters of renivillan and Syna, spirit hat be prepared in high yields from  $+-\sin(x)+\sin(x)+\sin(x) = \sin(x) + \sin($ 

In a promillimites of e-aming on rellance with e-AFA are dissolved in 19.7 ml association by adaption of 0.5 ml 10 millimates of triothylance, as a the fitting to the first or -4%, because 0. To this solution is a dissipated The part of which there is an a first plant of the problem and inting it is a second of the part of th remperar in a fine reaching mixture raises to make the temperature, the rejective amountumentarias cormed 1.7 g, a millimolest is filtered sif.

The a 10 millimoles of <u>resminopenicullanic and</u> are dissolved in 11 ml of emboring in the property of the pro mornyl milet programme is a rise in price under dry himster. The mixture is

Figure 1. Further, at  $\pm i$  , a greek of and is then heaters to a x temperature and times a for k much to k

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thorough of the entire perspect of the proposite of the first of millimites. or deputypy. - . - only - - 1, -, . - arrivago spholan bissilved in Lombon briften are asset under thy note dens Stirring in continued for looping estates. and Surgequently to the finance of the temperature. If him my render wis added. The frietny.ammonium dhioride tirmes is separated by dilifation. I drin: said filtration part of the product is lost, but the filtration is normally unnecessary when the product is to be used for further reactions.

stirring. ..40 ml to millimoles; of 2-onlord-1,3,2-thiadwaphospholan in 2 ml ary abetonitrile are added dropwise under dry hillbyen and at a temperature of about -40.degree. C. Subsequently the solution is stirred for about 1 hour at room temperature.

1.33 ml (10 millimoles) of diethylamine are added to 1.08 q (5 millimoles) of ningpeniall anic using suspended in 10 ml dry abetonitrile. After stirring in a mitrown armsghere for 2 minutes, a clear solution is obtained.

## 1.11 1.1

It a suspension of 1.1% of finillingles of  $\frac{1-AFA}{1}$  in 15 ml of dry nethylene whilering are added 1.4 ml old mightingles of triethylamine, and the mixture is stirred at room temperature until a grear solution is furmed. The solution is tooled to -40.degree. C, and 0.45 ml of millimoles) of ethyleneoulorophosphite issolved in 4 ml of dry methyleneobloride is added under dry nitrogen. The mixture is stirred for 10 minutes at -40.degree. T, 11 minutes at 0.degree. That is ningles at 15 minutes at 0.degree. The minutes at 15 minutes at Principly of the selection dissolved in a mile morthylemetal wide is added. The righture is stiffed for 3 minutes at four temperature, and subsequently the precipitated this oplania hydrochl ride is filtered bif. The solution is emporared to form a hard, pale yellow oil.

l gor <u>C-AFA</u> is suspended in 15 ml of dry methylene chloride under nitroden. To this mimpure are added 1.42 ml of dry triethylamine and 0.61 ml of Trinsthylphlorostiane. After stirring for I hour the reaction mixture is collected to -followings, and a solution of 0.57 ml of september of mixture is explained to -following fifth in finite in five perhylene onloride is added an quase. When the affirm a solution is the or limit is stopped, the mixture is stored to a formules, and the solution is ten to the or limit is stopped, the distance of affect, and the tractory, are commonly to be considered by increasing the first one. The remains associated to the considered associated as a considered associated associated associated as a considered associated associat normalism. The remark discretized in the truth to Frein 1. The first of the មុខស្រង់ព្រះប្រការ ខាន់ ស្នាស់ស្រាប់ នេះ មិនស្រាប់

IN Note: the millimotes of the elements, ephonyl algorithm in the Bol are then as a form of the first property as a first property of the state of t The first of the second and the state of t

the important which is in it is a summer with water. The organize have in opperate manufacture appears proved to warned twice with it is not definyle to fill the comparate manufacture appears proved to see that the comparate manufacture and the comparate manufacture manufacture and the comparate manufacture manufacture and the comparate manufacture noire while stirring. Coloring is untinued for about I hours while lowering the temperature to Elwerney. A. Finally the reaction number is left to stable overnight at the green. The precipitated depositemental enaghtous stops who is separated by first and on any wagnes with water and surgestates. The warms Free of the tris separated in the minustral and the pitch butylaretate and the pitch as the pitch and the pitch as the pitch as the pitch and the pitch as the  $_{\rm H}=$  value of the age of phase is amosted at 4.5 with the thylarine and the column of the rist in 0% reduces in terms of the fill of the 1 l, l-simeth wyerhane are assed and the mixture is stirred while being i lead to be green. I give a period of an union burs. The nixture is left to stand overhight in a ferrigerator at figegree. I. The precipitate formed is separateu by filtration, washed with water and dried in an extrator.

4.33 g (21 millimoles) of D(-)-phenylglycylchloride, hydrochloride are added in particus over a period of 1 minute to a solution in methylene chloride of 2. millimiles of trimethylsilyl-6- ethylenephosphiteamido penivillanate preparet as associated in Example T and without recoving File-nylars of the file, of a temperature of linegree. T. The progress of the reason of a fallowed by penthillingse intraction union after a period of D .degree. 3 shows that a yield of above 70° has been obtained. At nours at this time the reaction mixture is poured into 100 ml ice-water, and after stirring for 15 minutes the reaction mixture is filtered. The water phase is covered by 20 ml ethylacetate and the pH-value of the water phase is adjusted at 2 with a NaOH solution. Subsequently, the ampicillin formed is precipitated as a sparingly scluble salt with .bota.-naphthalenesulphonic acid while raintaining the pH-value at 2. The reaction mixture is left to stand for 1. notice at 1.5 areas. Thank as subsequently illiered and the residue is washed with ... I I Hall and staylabetate. After drying in vacuum "... I white  $rac{ ext{apple}}{ ext{constant}}$  . Deta. -naghthalenesulphonic acid s alt corresponding to 64.5 of the Theoretical amount are obtained. A high-voltage electrophogram showed one spot with mobility identical to that of authentic <u>Amploillin</u>. The IR spectrum was identical to that of the .beta.-naphthalenesulphonic acid salt of authentic mpirilian.

norm:

1.10 in 1. million less of <u>1-amin projected alleged</u> and its solved in a milliony alleged the contemporary of the addition of 0.8 ml (40 millioncles) of trigging time, 1.30 ml (10 millioncles) of trimethylchlorosilan are added impulse and the read in mixture is stirred for 1 hour at room temperature. At -1 decree, 0.00 or millimales of ethylene chlorophosphite dissolved in 2 ml dry alread lefter chloroform are added dropwise. The readilish mixture is stirred for 1 hour at 1.degree. 3.

## #213:

emiliantics and fully and pyrodias by the thirthe This is the replane of illimites and like of pyraine hydrotil for are dissolved in the following nethylene this is an heated to reflux. A court of contain less to the obligate in the relative settylenes of any nethylene childrene salidate is added during 40 minutes. <u>Encymptic</u> titration 1 minutes after the addition is applied a snows a penicillin yield of 30, while titration are or one and two cones were above 60 minutes. noirs both shows fill yield.

## BARR:

egen.
4 millimgles of N- term.-butowyparbonyl'-D--T-.alpha.-phonylgly-unc
trimethyledlylester propagate from 1.71 a 4 millimeles of
N- term.-trimethylester.pyl-el.- -.alpha.-phony.alpha.phony. If ml of chloroffer, ...
nl 4 millimeles of triethylamine and ..hl nl 4 millimeles of
trimethyl-unlargellam by starring for 5 minutes are added to 4 solution of 4

The control of the co deluned hydrochloric sold and twice with a solution of sodium hydrogen nyar (ml.:1s asii ana twise with a silutiin of sidium nyar spen farhinate. The solution is arise; were belong as a silution of sidium nyar spen farhinate. The solution is arise; were belong as a said and evaporates in various to item an arise; and places. Note that are spending to the side of the side of the side of the second spendings. The second spendings of the second spendings of the second spendings of the second spendings. gina. -phony. by ty. et. i - reph-re-en-levier Eylete.

## EMB:

Ta a saideith at 10 mllimaies af oring only slight a reconstruction of the spirit and in the property of the property of in Emangle () from Life a if <u>g-AFA</u>, in any metny tene sulfitted and added 1911 ; logillimiles of phenomyaretic acid, and the fixture is stirred at room temperature with any Sir publing through. After a reaction period of a hours at room temperature the reaction mixture shows a penintilin yield of the Ky empyrature it traction. The reaction mixture is moled to ".degree. ", and i of the pyrodime are added to lowed by IP of of dimethylsulfoxide, whereaster the reaction mixture is possess into ETE of the cold 1. MaCl solution and reaction mixture is possess that the cold for a solution of the period of the cold of the period o stirred for 30 minutes. Then 150 ml of ethylacetate are added and the pH adjusted to 2. After 30 minutes the phases are separated, and the water phase is extracted three times with ethylacetate. 25 ml of water are added to the combined organic phases, and the pH is adjusted to 7 with KOH. The water phase is separated, 150 ml of n-butanol added and the water removed by azeotropic vacuum destillation. The crystalline crude product thus precipitated is filtered off. Yield: 3.16 g  $\{51\%\}$  of a purity of 76% determined by panicillinase titration. The white, physialline product shows a characteristic absorption in the IP spectrum corresponding to that of the potassium salt of The myset sylpon villin, and the MMR spectrum also shows signals which are hama Heristitus sii oraștund.

## 14 4 11 4

.el a 4 millimples of phenomyarenic arid is added to a solution of 1,2,000-richlorostnyi-S-matnyi-Tubeta.-Jetnylenephosphiteamido - regh-s-e m-4-parboxylate in abetomitrile prepared as described in Example 11, except for the filtration to persue the precipitate of trietnyl ammonium chioride. The mixture is attrived for 1: hours at room temperature. The reaction mixture is tion purpose in the water and extracted three times with ethylanetate. The organist training been are washed three times with 2 M sulfuring and and three times with saturated sodium hydrogen carbonate solution, dried over Mago, sub. 4 and evaporated in vacuum to form an amorphous powder:

4.76 g of N-parhobendowy-0 - "-phenylylyppine in dry methylene officeride at room temperature are added to the product (6.5 g of benzyl H-ethylenephosphiteamidopenicalilanate) of the roduction described in Example 3 un ter not rigori. The nombine is stirred for 4 hours, evaporated to dryness, along the first of the control of the state of the state of the solution is drived that the solution is drived the solution of the solution of

## B. 11 B :

1...1 g [4 m.] [1 moleco of M- tert-butomy marking [4 - D. - 4 alpha. - phony [ j. y of tetro added to a solution of

or, type the resemble secting the the setting that also be thy lementic applies and as the replication property with the second control of the property of the control of the property of the control o er akur are washe fithese tirek with a William i ayu ana three tirek with ar aasen arang iya biring hate iji. Dili, arek ten Mahasud 4 ani the first that the state of the

ross.

I so a of dearth policyless, a sola are dissilved in TS., milyf abstractibe by quantion of left oil or type-hylarine, and the solution formed is booled to end the present in Assilvation of 4.4 oil of emplementary possessions in Assilvation of 4.4 oil of emplementary possessions of the abstraction of the action of th on a construction of the control of Carrie on the state of the state of the

A solution to the triethylammonium sait of deernylane phosphire amidaponicillania acid was prepared from 2.16 g [10 millimoles, tf Framinipening and and in the marker described in Example 1 and the priethylanmonium chloride formed was removed by cultration.

The MMR spectrum (M.sub.) SW of a sample of the reaction solution showed that all <u>e-aming-continuence abli</u>thed been converted into the corresponding emplete she siniferral directand, and the following characteristic signals were pristing:

has the meaning defined above with a salt of  $\frac{6-AFA}{2}$  or of G-aminobephen avid or a derivative of said acids.

The rugling constants C.sub.P-N-C-H, C.sub.H-N-C-H and C.sub.H-C-C-H are onsistent with these found in literature (for F-M-CH.sub.3 compounds are normally found Jusuk F-H + 8.8 - 25 Hm (Jackman and Sternhell: Applications of Muylear Mashetis Bosshahse Spestios topy in Organis Chemistry, vol. 5, p. 352 Class . The doupling J.sub.H-C-C-H = 4.5 Hb is also found in the simal doublet from the proton in the S-position in C-AFA. This pattern in consumption with the signal of the 3-hydrogen and the infrared absorption trequencies of the careonyl group in the 3-position which are consistent with those normally found in v-AFA derivatives, is a conclusive proof for the presence of the structural element: ##8TR5##

## - -

Ares de Albe

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provided the first of the content of the following periods and following the first and the first segments of the first segment of the first segments of the first segments. generatives with the cyds. Albride if Lernesylstyling-chlorine and derivatives thereof naving a supstituted phenyl group, whereby the said abid choride is eptained by reacting the substituted phenyiglycine with reagents like phosphorus pentachloride, thionyl chloride and phospene. Although improved processes for the preparation of  $D_{-}(-)-Z_{-}(p-h)$  droxyphenyl)-glycyl- $M_{-}$ loride hydrophloride and the prystalline hemidicxane solvate thereof are known from  $\frac{1}{2}$  green part No. 1,466,637 and No. 1,460,915 the adylation of  $\frac{1}{2}$  HEA or NAR TO CA or its 3-methyl modification with the above-mentioned adylating agent aid not hitherty lead to results aimed at, mainly because either the product formed was too impure that further recovery of a product of the required quality hardly appeared to be possible, or the starting d-I- p-hysecocychemyl -glycyl phloride hydrophloride of the required quality spurity) is only available for economically unattractive prices, if at all.

## Hark:

A process for the preparation of amovicillintrinyarate is also known iron published German patent application DT ZellZee comprising the anylation of 

## : H:

However, in the preparation of Devel-1- p-hydroxymbenyl eglynyl chloride hydrochloride according to the British Fat. No. 1,40%, 416 and British Fat. No. 1,466,63%, phosagne is used in a relatively difficultly manageable process in which a solid is reacted with a gas. Such a process is extremely expensive in a number of countries with very stringent safety regulations, if indeed it may be applied at all. For the same reason, the process described in British Pat. the applied at all. Its and case them is the propagation of the state of the control of the state of the stat o necessario no so o successario no constante en en el giólico en se regisal es constante en el perceatives natural their three names else than in the testion.

## : . : : : :

less attractive reatures or this process are that the process is carried over these and restricted two lates of this spiritudes are than the process is tailing at low or neutrations, that solvents become nixed so that recovery thereof recomes more difficult, and that, when adding the dimethylated unide the solvent filters, is a first that a restricted process of the solvent solvent at long, it will be a first that a restricted process of the solvent solvent and the solvent solven

For norm 10, a number of papers applications and patents disclose preparation permods or valpha. - aminoabyl-penibilianno acid debivatives by apylating <u>r-ALA</u> with mixed annydrides derived from modified Dane salts of 7-2-amino- p-hydrowyphenl -acetic acid, such as those described in German

parent Wightham on the CD . I.e., which is a property of the set N . ., expected and which is large N . I.e., N and N . I.e. N and N . I.e. N and N . I.e. N are substituted in the set of the The control of the present invention, and marking, the lank sayes appeared to be avaluable un efinimically inacciantive quantities, it at all available.

The organism Application for Division 1941 Forther Sistings the protestion of the case against a great and the feether than the case against a great and the feether than the case against a great and the second and the case against a great and the case against the case against the case and the case against the c The transfer of the control of the c theresi should, in a number of cases, load to improved yields, as appears, such as from British Eat. No. 1,288,749 disclosing the preparation of oncernediate organis: Dane penicillins by reaction of M-AFA and those Ri-functional silican compounds. The organosilane derivatives are adylated into <u>apply thin for example,</u> so that an expert from the contents of this patent will expert that the use of the ordanisilane penicillins less wiked na Company of the second interesting years in the steps of the property of the property of the company of the c e some, this experience is the supplemently notice continuately initial emperature of a constant

Although it is further known from a number of patent applications such as Japanese Patent application No. 49-114687 and No. 49-048892, British patents No. 1,367,342 and No. 1,362,255 and German patent applications Ser. No. 2,462,649 and No. 2,621,614, to prepare amoximillin from 6 ATA and p-hydroxy-phenyigiveine or lower alkyl esters thereof by encymatic acylation, the processes of this type are also unsatisfectory for the desired purpose in the of the yields intained and or the presence of the acylating encyme in the amominillin-oyntaining stlution obtained.

It has been found that the way in which the silylation is carried out is very important for the final yield, and the silylation is preferably carried out in dry methylene chloride containing 2 to 3 equivalents of a tertiary amine such as trie hylamine and an equivalent amount of TMCS (about 2 equivalents for anomivillin and ownamowil and 3 equivalents for refatricine, in such a way that the sime, recorded by a pH electrode is adjusted at the chalof the reaction at a constant value of, for example a pH spale value between but and min in, it a best moder pH moder type TTT1, and a T. , presentily e. And T., file Federmeter pH meter type TTTL, C and a Federmeter W 14 to electrode, at a Federmeter W 14 to electrode, at a temperature between 15 degree. and if degree. C. Therefore, disilylation of e.g. of <u>v-AFA</u> or "A.T" TA is preferably carried out with practically balanced mutual amounts of triplower alkyl halosilane, such as TMCS, and tertiary aminy such as TEA .

And the state of the first of the first of the solution of the administrate as the particle of the solution of the administrate as the particle of the solution of the solutio . to Estadegree. 2. is reached, whereafter the reaction mixture is stirred for a further 1.0 to 3 hours. An expess of the formula I compound is preferably employed, the expess in the expension on the nature of the substituent of the Through group of the emphalosporanic nucleus. For the preparation of amountailin and perainfail a small expess is sufficient. In surparation of amount of the compound of filmula T will be recossary.

NAME OF A STREET AND A STREET OF THE POST AND POST AND ADDRESS OF THE anglation problems of the hypermical area grevious and selection slighting of e de la la la la composición de la com Las la latignas de la composición de l constituted solution of the properties; over the same of the equipment this will farm ably incluence the curpor in biles \$42 bat the the use lift a

properties a rather difficulty renapeared professions which has not an only despite the arrangement difficulty renapeared professions which have been as extremely expendive in a number of a furtiles are to very stringent safety as relations, if indeed permission for the ranifactors can be attained at all, the use of carses an interpretation of the ranifactors avoided; the desired final profession as approximately attained and large expensions as positive attained under available results regulate has white at the area time, the district of positive to the carse time, the district of the positive relationship and the relation of a least of the rank time that resolvery is a strength when the rank are the rank and the rank of undesired and the expension of the rank particles and the relation of the rank of the rank and the relationship and the relationship and the relationship of the rank and the relationship and the relati

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integral to the content of the content systems for an integral of the content of

## FS1R:

As in industrial processes the application of the roughly dried solvents and in lane salts of very high purity is an ideal that will never be realized completely, a solution excess of the starting lane salts and it observable, only introduced are preferably used. In the preferred explainments of the process of the present of the preferred expression, starting through the presents of the presents of the solution, as infollows that they improve a starting through the presents of the solution of what by a decrease mutual and units and in an another than the formal and the special of two equivalents with the formest of a constant and the with N-machylmorphiline as smallyst; and a consolvent selected from N,N-dimensional processes. N-machylpyrrollidene, N,N-dimensional processes, and tetramethyl urea or mixtures thereof, and methyl chloroformate, while the solutions of the in situ prepared silylated makes and and the nixed analysis are pre-trained to the starting of the instruments. It starts to seat the covering an xidilingly known methods.

## B.11.11

If  $\frac{1}{2} - \frac{137A}{12}$  is a new quality of with an expression as strong terminary arine bases such as trivially larger and a livent such as retrivials will rise an interpretable to the configuration of solutions are such as a livent and a such as a livent as the configuration of the configuration.

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The T-ALTA was applied by a masking a title profile to the title to the starting of the starti

om to distinguish and and different appropriate to the challent and after hillar.

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to do interpretation of the Western who we then into a 1 linear to now ever and to be a confident product of the western theorem . With estimating, 4 miles is the estimation of the structure of

## EFF:

In a notified atmosphere, Field of 41 nm less of i=A1A were suspensed in 15 or it any methylenes of rise and 11.0 n  $^{-1}$  such as the triesthylamine and 1.5 n  $^{-1}$  on 168 of trinscription is will answere about suse greatly. This mixture was reflect with storic in it follows and then was to led in an 168 path to the path

## 1144:

With vir rous stirring the turble solution of the lane annywhide prepared in step A and to left — 1. degree. A was alief all at need to colled solution to the silvlated <u>--AiA</u> obtained in Step B and the mixture was stirred for a further of blocker in a lee bath. Then, the loe bath was removed but stirring was continued with introduction of nitrogen until room temperature was reached about 40 mindres. The mixture was poured into with cooling 75 ml of ice water, whereafter the pH, which reached a value of 2.5 to 3 was adjusted to 1 to 1.0 with a negative hydrochlorin acid as measured with an Electrofact KCL electroie of 1.5 to 1.0 with an AgCl electrone.

In substantially the same manner as described in Example +, amonicillin trinydrate was ditained in a yield of "foot with a merturemetrically reasoned purity of +8.5, a prilogically reasoned quality of the and an optical rotation [Lalpha.].sub.Dosp.Dosf +880.degree., starting trum 48.5 mmoles of patassium D-Lalpha. | 1- tarbéethoxypropen-8-yl/-amino-p-hydroxyphenylasetate in the new forethylls butylketone and to mloof tetrahydrofuran, "... in mloof N-rothylm uph line, 44 monless of tetrathly rotamate in 15 mloof of thylle butylketone, 4 cm less of tetrathly miles in try methylene onlocket, as on less of this try methylene onlocket, as on less of the patalogical residence.

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## 1811:

The statement of the content of the content of the Emergence, an efficient terminal terminal content of the con

grapha in in this is may restry take that is important the first triving among and The first of the state of the second of the

In a detantually the same panner as describe; in Emargle e, Amemicilism Talogorate was stranded in a years of some naving a negotioners cally beasure:

The first of the control of the cont N-metnylrusphiline, 44 mriles of ethyl shlorifishate in 3. ml is setnyl isuputýlketíme, 4° proles si <u>kekik</u> ih ok orl of mry metnylene shliviaé, 6.... po les of trietnylamine and 62 molles of trimethylshlivosilane.

to for  $\frac{1}{2}$   $\frac{1}{2}$ pis trimethylsily: -urea, the mixture was refluxed for about 2.5 hours and the mixture was then occled to 20.degree. C. The "pH" reading, on the scale of a Padiometer pH meter type TTT 2C, connected with a Radiometer GK-24°10 clestrode, was 6.3.

## DEFR:

In the same manner as described in Ewample 13, 49.3 g of amoxicillin tribyurate having a purity of 97.70 were obtained by reaction of neth my has held

1-.alpna.- 1-parksmethomypropen-2-yl;-amino-p-hydromyphenylacetate and 38 g of reasonspecialilania array previously silvlated with 72.5 g of pis trimethylsilyl, acetamine instead of the bis trimethylsilylyurga.

## DEPR:

b' Bilylation ur <u>6-A&A</u>

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· 이 제 기업성과 회사 역회관에서 기계 - pl ni perbylene inlighte. After widition in 48 n. It tristing access an articut temperature and ander stirring, a miler tringthy, he testians are about in about 1 minutes at a temperature of the needs. There are . After additional stirring for 1 hour the "pH" value is adjusted to a final value of  $\epsilon.7$  by the addition of 4.9 ml of rimethylphlorosilan. The mixture is socied to -40.degree. C.

In the same manner as described in Examples 13-15, 55.3 g of amoxicillin Tribydrate are optained in a gield of fl.5 having a purity of 99.5 according to a tribydrate are optained in a gield of fl.5 having a purity of 99.5 according to a trib percurbs tribuly be expect posity of fele , and an eptical retails: ,...), D....., sub... (...sup.) od +900, stanovno fram 09 a či podasšium Note that the extension problem is the second

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In the ware manner as postured in Examples 1:-10, %.i. i or an archilling troby have are sitains in a grelier will having a purity of self apporting to a by bowylarine method measurement, a biologically measured pority of 4- , e mencunomedrically measured purity of er. " and an ortical resigning (.alpha.).sub.w.sup.D or vall, starting from at a of potassium

In alpha and letter methodype peneley, marin epenyor mygnenyla estats in more than the more and the plant of the structural estates, and if Menethylene the structure, is not a sethylene the structure, as not a sethylene the structure, as not a sethylene and as not a structure is the silane. The "pHH" makes reasons a with a Padrimeter pH motor TTTLD, and a Padrimeter GK as 10 electrone was admissed at 4.7 at the end of the silylation reaction, while the structure of the silylation reaction, while the structure of the silver and the silver pHH.

# 1818:

In the same manner as described in examples 13-15, anomicillin was prepared in a 51-acylation yield starting from 56.1 g of potassium 2+.alpha. - 1-carbonethoxyprypen-2-yl -amino-p-hydroxyphenyla setare in 471 ml of nethylenethliniae, l of or N,N-domethylicomanide 1.5 ml of N-methylenethliniae, l of or methyl militorrate, l of or l-AiA in all of N-methylenethly of the same and of of orthogonal residuals. In the pre-region examples was activities at a constant the same epippent as in the pre-region examples was activities at a constant of the silviant of reading examples and reading and of silviates  $\frac{l}{l}$  were pre-recited to -41.degree. 3. and readted at -71.degree. 3. for 2 hours.

## DEFU:

STEP B: Silylation of K-AFA

### 18811

STEP B: Solylatick of F-ALA

## DEPU:

STEP B: Silylation of 6-ABA

# WEST

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## B.11 H:

Anylation of the dearth or up to a replacity of increasing group of a penicillin end, and or placity of an end of the chaming group of a penicillin stape, as a final feature of the chaming group of a penicilling stape, as all whose constants periods are supported to the tree and rate and the tree and transfer and the tree and transfer of the tree and transfer of the tree and transfer of the stape, and the stape of the

## F.11 F :

ther iseable and various derivatives or close the corresponding an likes, i.e., arises if a presponding arises, the angue notioned which is a meries of a quasiarisation temperated ring which contains at least two notions at the example, if an imitable, pyrabole, triangle, behalfidable to behind this learning. An one iseable derivative of a substituted phenylglycine of Formula fill is a N-parbhayanhydride (Leuchs' anhydride). The group which activates the parbhayl group here also protects the amino group.

## 4,114

For example, THATM territerary Lester or eHALA territerary Lester can be reached with a compound of Formula TO ###THEL## wherein Firmula in a protection in the minus of the minus in the minus of the m

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is and in a responsive of the release terresponds to Ferrula I, into in one of Ferrula I, into in one of Ferrula II, into in one of Ferrula II, in the second of the property of the property of the property of the second of the

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The or its wind appreviations are used in the Examples: IMF simethylformanduc, -ATA Tearing rephal sporance acid, --ATA---aming point illandication.

Interpretable sylvanishing as THF terral particular,

But tear terral properties by the FMU tears with mylelerathylvingly.

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A restrict to the restriction of the second section of the section of the second section of the section of ganalyzed anylatiji ji toe parest soeta. -lantam with am antivated aerivative is the stae busin agid wherein a modulator, which consists of one or more compounds different from the reactants and the reaction product and which suppresses the hydrolysis of the activated derivative of the side chain acid and the desired primuot more than it suppresses the synthesis of the desired product, is added to the reaction mixture, at the reginning of the reaction process, in a concentration from about 1.2 to 101.times.10.sup.3.mu.m.

## 1373:

The present invention relates to an improved method for enzymatic adviation. in particular, the invention relates to the preparation of .beta.-lactam antibicties by ensymatic asylation of the parent amino .beta.-lactam moiety with an applicating agent which is an activated derivative of the side chain arid.

### BSPR:

<u>Encyphile</u> production of semisynthetic operateless and another took by acylatica the parent aming .bera.-lastam numbery with the side chain abid or an aminates being ine, aun as an amile or an ester thereof, is known plus from Mass German parent application having publication No. 1,163,79., Austrian Farent No. 143,800, Durch parent application No. 13-14139, West German parent application having publication Nr. 1,6.1,618, Furgream patent application having publication Nr. 388, 711, international patent application having publication Nr. 388, 711, international patent application having publication Nr. W. 41 91001 and from international patent application having publication No. Wo Movil225.

## ESER:

Table of the second second of the second sec IN The lamb with a latter can be published and expectablished to coming the  $\frac{1}{2}$   $\frac{1}{2}$ Firstin a rearrangement process before the hydrolysis step).

The particle of the American for the particle projection of the at-last and an article of the attention of the particle of the particle of the attention of the article of .erra.-lam er. Them, when the write of the site than arra is used as toplating about, some tree stde chain avid and an equivalent amount of appoints will be generated in the reaction biwture as a result of this hydralysis. Dirilarly, when an ester of the side chain acid is used as anylatina agent, some free side chain acid and an equivalent amount of the alcohol contrasponding to the ester will be generated in the reaction mixture as a

result of the by modystr. Also, the decired product of them by droughest to dominate tree wite chain and and the parent applications as a

In the com, empressingly, even found that certain blaulating, i.e. the plant × . ng nam na da na ing ang manta and the readtion product, can be added to a the many of the control and the control of the cont the side chain activits used as applicing agent-rand in the designs product to suppressed more than the synthesis in the lesined product.

And rilingly, in the createst aspect the present invention relates to a method for rilingly, in the createst aspect the present invention by the present of anyletic notice particles of the side main the particles of the side main and where he were a first anylating are made in the identity of the invention of the spring of the synthesis of the spring of the synthesis of the resident product of the resident of t maired projurt is added to or present in the reaction misture.

Examples of .beta.-lastam antibiotics which can be produced by the process of this invention are approxilin, amovibillin, tiparpillin, pefablor, defatrizing, refarats), rephradine, rephalexin, refadrowil, rephaloglypin and gephaltinik.

The adylating agent to be used in the method of this invention is an activated derivative of the side chain acid such as a lower alkyl (methyl, ethyl, n-propyl or isopropyl) ester or an amide. The amide can be unsubstituted in the --NH.sub.2 group which is preferred, or it can be substituted by one or two lower alkyl groups--identical or different--selected from the group comprising methyl, ethyl, propyl and isopropyl. The derivative may be used in the torm of a soil for examples the hydrophloride or the substant Evamples the form of a salt, for example, the hydrochloride or the sulphate. Examples is side that arius are <u>D-rienylylytine</u> or D-r-hydroxyphenylglycine.

Françier of parent amino destablished which can be explained by the method of this invention are required by the method of each invention are required by the method of each of the each o THACA and Than inches oblices - 3- septem-4- subowylame.

The amount of podulator to be abded to the reaction mixture in order to the amount of podulator to be abded i.a. on the identity of the modulator and added the inclusion of the podulator and there are not to this to the about the charge of the claims. It is this important to not two can be indeed to the examples and in the claims. It is this important to not two that at the high notion of the populator will prevent the desired that are not included the continuous translation of the reaction mixture is so low that in does not include the water activity in the reaction mixture. In any case, it will be lower than that of the reactions, preferably lower than 100 pm. that of the readmants, preferably lower than 100 mM.

the Short to be need in the bridges of this intention has be and winder FFR: The graphs of the reservoir in presenting dark on the present and the been which since the manual straightful the reservoir in presenting dark on the present the action of the control of Walfari day, my manak manag kangi, Adi bilah west berlah pangi was so that we have a second control in a specific period of the second control of the s

Wanthur has diffic him pean patent application naving puller D.A.D., only, of y. M. Hypers difficulty of the Administration having puller 4 can be subscriptly as a subscriptly of the Administration having publication for the first configuration for the first configuratio resulting and the even which ye will appear to the engine of the engine

In is presented to the class of a second of interest of the second of the present of the second of t Mannheir Brill, Bernany, in her the trade hame Enhydel.

The solutility of the adviating agent such as the <u>leptency by the</u> if The solution explicitly the decidative of a difficult for the fill mixtures as the tribed in higher to 1, will vary with the lightity of the decidative and with the time set and the result have my linear place of eyetem is used in the examples, the solubility of the nyintenderide of 1-menylary time and 1- is typically approximately 480 mM. However, the solubility is very dependent on the salt components in the solution, as well as on the pH value and the temperature of the solution. In some embodiments of the process of this invention, the initial reaction mixture is a slurry containing undissolved abylating agent and or amino .beta.-lastam, which will dissolve partly or fully during the pourse of the reaction. The theta, lastam antibiotic formed cay free ignistry to his the reaction and, also, the hydrolysis products of the anylating apont sime as 1-chenylaly one and 1-r-nyiroxyphenylalypine, may presignate. Hence, in some cases the reaguing mixture will be a slurry throughout the duration of the reaction.

The amino .beta.-lastam, for example  $\underline{6-AFA}$  or 7-ADCA, used in the process of this invention may be obtained by enzymatic hydrolysis of the fermented penincilling or regular sportus (for example penincilling, penincilling of regular sportus), or the regular peninciples (for example U-DOA and High the control of t solution of the mean air-only with to further purification or dilution.

## CEPR:

Generally, the reaction temperature of the process of this invention may vary between about 3.degree. C. and about 35.degree. C., especially between about 7.degree. C. Temperatures in the range about 1.degree. C. in deares. -30. deares. C. may be preferred for convenient operation. The pH rains which is my inal depends in the type and purity of staymo. Using the second of t the preparation of a smithlish, a pH value in the range from about 8.8 tm about 1.4 is preferred. Cintrol of the pH value may be used. Suitable reaction numes are from several minutes to several hours, in particular from about Lour of about a nouse. Suitable <u>endyre</u> concentrations may be finds, about 1 7 pl to about 100 mpl of me necessity of <u>chappe</u> activity, see set who

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Twing the rich a greathing this invention, undersity him years of the Session a great at #lamam and the first can be carrained. The first give as any strained a The state of the second of the and the stanting among decta. - Lagran, the pH value, the encyme and the is noting and amount of hearth type.

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D-HFBA is D-p-ny manyyhenylalyanna smide, D-HFB is D-y-hydraxyyhenylalyanna, e-AFA is e-ghin lenibillahin dela, Amom is amemicillah, Ehem is phenomyaretic ana, ana inyi ing ponyia estimama.

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Variable. As we use the equation well stry of As x is small by unit Variable  $\sim$  1-HeV. is the instruction of this fit instruction was into a solution of interesting and interesting and interesting in the solution of the solution

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The following withit is a penticular 3 appraise artivity is used the into the amount of entype that hydrolyses per minute 1 imalmyTe apparation 3 independent attacked and tricks 5 penticular 3, 1.2% sodium prisphate suffer, pH 4.7, landegree. 7 .

The rate X to be the rate the number of a less of 1-HE Value specifier rate of Amount provided For practical uses this can be transferred to Xel-rates
1-HE Control Amount of the ray attention about any time of labour and "males Amount" is the modern amount of Thus, if M is 1
is the modern amount of Amount resent in the realting mixture. Thus, if M is 1 this reads that they the desired synthesis takes place, no hydrolysis. If X is a, this means that C=HF and Amix are firmed in equal amounts on a molar kasis. If X is A, this means that twise as much C=HF as Amix is present in the readtion mixture on a polar basis. The ratio X can be calculated at any time during reaction, but in the following examples X is calculated at  $t \hbar v$ resistion stop time, which is defined as the time at which 90 theoretical yiels of Amon is present in the reaction mixture (based on the inserted ambunt of  $\tilde{\ell}$ -APA . Square brackets are used to designate molar dungēntrāticns.

Retention times in minutes: 2.6 (D-HFG), 3.5 (D-HFGA), 5.0 ( $\theta$ -AFA), 13.5 (Amori).

In Examples 1-8 the following standard conditions for encyratio amenicalling synthesis have been used uses patent application No. WO P201101 for further  $i^{\omega_1} = \dots i^{\omega_1} = i$ 

Curing the result us, the yE value of the results mixtures was kept constant ly titration with OM adjustra grid.

## 12.25:

A standard synthesis | immobilized penicillin 3 acylase from E. coli; encyma desing Fig.Timin was garried out with no Phox added. The Phox level was  $\frac{\pi}{4}.6$  unit. We in the reaction numbers due to a residual Phox content of 1.2000 which the given the first out of  $\frac{\pi}{4}$ .

## 

A štaniari sunthesis (impuriliče) penitillin (i avylase trom E. voli; dudyre dising field Timi was captied out with no Engl added. The Fhom level in the reaction mixture was J.E. wor.M. The results are reported in Table 1.

For Airporent imporilized Len 3 anylase preparations were used: a ing Pilto i penialilin i advisse from F. adi, eng<u>re</u> desina é.c U ml; p anar se a ad a con a librate, iostor l. . U ml; a limbbilitate obtained from Bengiate, i den l. . U ml; and i consellicate distained from Beshriner Manheir experimental preparation, a since II. Tall.

of limits from Planylass propagations were distanced from Table over, art. M., These, was him. Tool, and from EBE, was bill Unit, an <u>enounce</u> distance of ejug of Tori wore applyed in the two series. The results are replified in Tarle

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A standard synthesis form filtred periodilling anylase from E. of Hi, entropy a similar (0,0) was particulant with  $n_{\rm e}$  1-p -mandelling in a liquiditie of the English. sankar una level was elle unum in the reaction nimbure. The results disable:

A standard Synthes. The number Mannheir arm addition generalize graphs. experimental preparation, <u>in promo</u> and in 1. Ton. Was defined in with he office profession and a safety life filtural exercic description the seasons. boxtoni makarenda ekonomiak under ingarrengik katainga are reparted in Takie

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## PEFT:

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### TELES:

ncymatic Synthesis of Amswidillin Using a Fiwed Dosage of Immobilized Pen 3 Advisor and Varying the Phan Delicentration in the Readtion Mixture from 2.6 to

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<u>Encymatic</u> Synthesis of Amoxicillin Tsing a Fixed Dosage of Immobilized Ben G Applase and Carying the Phyl Congentration in the Reaction Mixture from Axim · > 1/- .ma.K

Engymatic Synthesis of Americallan Using Various Immobilized Freparations of Pen 3 Anylase and Carying the Phox Timpentration in the Reaction Mixture from 

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known at a Cymthesia of Archibillon Usine Tarylne Archits of <u>Encyre</u> and a Schetar for centration of Frex

### TEFT:

Eucymatic Synthesis of Amoxicillin by Using Soluble Fen G Acylase (Two Different Suppliers and Marying the Phox Consentration in the Reaction Mixture from 4.6 to 147 .mm.M

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Figure 2 Synthesis of Americallin by Using Immobilized Fen 3 Applase and arying the C-Thisphenesseria Asia Conservation from 2.75 to 2.3 mM in the teant i Mixigo

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side chain abid wherein a midulator, which is a carboxylic arid of  $\lambda$  to  $\lambda$ cark in atoms, and is different true the reactants and the reaction product is ather to the readily number, at the periodic of the resource process, it is necessary to the resource process, it is

gagai. <u>Engyra</u> Komat. W. F. Car <sup>1</sup>ab.

McSougall et al. Enlyme Microb. Teannol, 1982 vol. 4, pp. 114-115.

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### 1. 1.

The value of the outpoints of the thrent, is she preferably salve with prient about coally a computable independs or objects about soon as report these of acid, hydropromio acid, sulfurio acid, phosphorio acid, partario acid, citalo asid, fumaric asid, and the like.

In a narrant of many of the appraishment free penialline, the complands of the invention are end dently absorbed true the destrointestinal tract and are then, whise the nillence of phaymes, rapidly hydrolysed to the parresponding rree penicillins. This hydrolysis is an important teature of the compounds of the invention. It is assumed that the first step consists in a hydrolysis to the hydroxymethyl esters of the corresponding penicillins which subsequently descripose spontaneously to the free penicillins.

The compounds of the above formula VIIIa are new and can be prepared in distances namers, for instance by reacting F-arinopenicallanic acid with a ompount of the property setting to which R.sup.P. R.sup.P. 7, and n are as write a state. The reserving is preferably performed in the presence of an amine, e.g. triethylamine, and at room temperature or slightly elevated temperatures in an inervisition, such as dimethylformamide, whereby an inverse in an inervisit strength of the formula ##EQUIT## (an be isolated which, after conversion in ermediate of the formula ##EQUIT##) in the group I into an unsubstituted or substituted anine group, yields the try units of translationals. The conversion of I can be performed as described imposinted res. The grine group at the deposition of the penistilanic anid can to, but is not be besently, protector by well-known protection groups, is instance a trity. Hoth.

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Frocess for the two very of <u>angly plans</u> from a new are containing <u>angle plans</u> and c-animagenicallic acid <u>c-AFA</u>, in which a mixture of <u>angle plans</u> and <u>c-AFA</u>, with a pH higher than  $\mathbb{T}$ , which apart from any solid <u>ample plans</u> persent is homogeneous at a pH between  $\mathbb{T}$  and  $\mathbb{R}$ . It is subjected to a pH lowering till a pH lower than  $\mathbb{R}$ . It is reached, and the solid substance present is recovered. The process is in particular suitable to be applied to the team. In fixture which is obtained after the <u>enlymatic</u> adplation reaction of this with a phencylety of the derivative as adplation agent. Fure <u>ample plans</u> can thus section to a simple way.

### BSFR:

The invention relates to a process for the recovery of ampicillin from a mixture containing ampicillin and 6-aminopenicillic acid (6-APA).

### BOFF:

In the preparation of <u>amprolling with a ANA</u> being applated with a Tibling by walk the restriction of the amprolling and working up of the dearth of most Secare approlling to reneral.

## H.71 H.:

A process for isolating the <u>ampliciblin</u> pure from a mixture containing ampiciblin and minor quantities of <u>d-AFA</u> is described in JF-A-47030657. According to the process described in this Japanese publication, an acid aqueous mixture containing <u>u-AFA and ampiciblin</u> is subjected to an extraction with butanol or iscamplaboral, after which the pH is raised to a value between a and the product is recovered by complete boiling down and Index-topics. The interest of this method is that organic solvents that are such to the process have to be added. In addition, complete byiling down and Index-arrying is not unaustrially practicable. Moreover, the process involves topy to the same to a include it in the indexe-inferior doct.

### 

PR-A-fr4411 displises a process wherein ampirillin is recovered from a mixture or ampirillin and amino-penicillanic and by conversion of the ampirillin to the trially lance salt and recover the ampirillin as instribly lamine salt.

### 14.11.34.3

The content of the invent, in the temperature and property in referrally practicable for the second of the feather than a limit of the result of the process.

### 130

This is achieved according to the invention in that a mixture containing ampleablin and 6-AFA and having a pH higher than 7, which, apart from any actif ampleable that is present, is hardpendius at a pH between 7 and 4.2, is subjected to a pH 1 worths to a pH lower than 4.2, and that the solid substance present is converse.

### 30.13 3 :

if all the person and any constraint the pill of the provide the action of the fiver than the person and the pill of the person the mixture, after which it can be recovered. Besides <u>anguillin</u> the reaction survive somen contains other valuable components, such as for instance the Figure strenge contains other valuable complication, each as in the consequently served in grader to denote a consequently appropriate process in is consequently served in grader to denote the served served served to a value of least their conditions are also served to deach of least their conditions of a value of least their conditions of the served served served to deach of least their conditions of the served served served to deach of the served serv The state of the s 

The process according to the invention is in particular suitable to be applied in the working up of the reaction mixture which is obtained after the engrationary attended in which character is acylated with Chency divide and the life of extended interpretable in a start and next the contact of the content of the action of the action of the action of the content o my suppressively filtering, with isolation of impubilized <u>encypes</u> the or opposition mismore of an <u>endyma</u>tro adylation reaction darried out at a relatively high sH, isr instance a pH between .s and 11, in particular between 8 and 18, lowering the pH to a value between 7 and 9. Depending on the amount of D-phenylglycine (PG) formed during the acylation reaction, if desired, it is possible to remove first at a higher pH-value between 7 and ?--which is selected dependent on the mixture such that already PG has been rrystallined out and ampirillin has not yet -- the eventually formed solid substance, which nostly will consist mainly of FB.

In an ther end sphero the startler ristance used is the mixture obtained after an <u>entirely applicantion</u> reaction that ends at a relatively low pH, for instance a pH ketween T and t.t., preferably retween T.f and t.t., and after isolation of the solid substance which mainly contains the immebilized entyme and 

The fire what find position of the similar of the first one of the life of the similar terms of the first of in particular \*-1 .

The pH may be lowered in several ways in the framework of the invention, los instance chemically by adding an acid, for instance a mineral acid, in particular <u>sulphuric acid</u>, hydrochloric acid or mitric acid. Another passibility is for instance, if FSA has peen used as jugianion agent in the legistin bearing a disam seten of an extension has been used and the pH has peen kept The control of the co mortillate more referred gross in , in partirular thin-film evaporation; emploration in a spray tiwer; has receivable separation or electricallysis.

The optimize pH at which applied by is to overed depends in the \*optimization of the optimization of  $\frac{1}{2}$  and  $\frac{1}{2}$ 

The offers band and to preday which is a different of the pH at which the object of the photometric state of the part of the prediction of the part of

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The process according to the invention for recovery of pure apply. In introduction with regired animal of the planture of  $\epsilon$ -AkA and apply 1.11 obtained attention with regired animal of the planture of  $\epsilon$ -AkA and apply 1.11 obtained attentions after the planture of t

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In this interest in the used that is suitable as catalyst in the capital feather the engines that are known that the denotes a designations periodillic amidase and periodillic acylase. Examples of suitable engines are engines derived from Abetobacter, Aeromonas, Populagenes, Albaligenes, Aphanoblodium, Bubillus sp., Cephalosporlum, Escherichia, Flavobacterium, Kluvvera, Mycoplana, Protaminobacter, Pseudomonas and Manthomonas, in particular Abetobacter pasteurianum, Babillus megaterium, Escherichia coli and Manthomonas citrii.

# ESTE:

Freferably an immobilized <u>Engyre</u> is used, since the <u>encyre</u> can be easily is later and re-used then. Immobilized <u>encyres</u> are known as such and are summer lally available. Example of suitable <u>encyres</u> are the Escherichia colinguage from Bachringer Mannheim SmbH, which is commercially available under the name 'Encyrel.FTM.', the immobilized Fenicillin-3 acylase from Recordati, the immobilized Fenicillin-3 acylase from Fharma Biotechnology Hannover, and an Escherichia coli penicilline acylase isolated as described in WO-A-ALFILTED and immobilised as described in EF-A-LILAFI.

### HSFR:

The equipment is doubt ion reaction is mostly carried out at a temperature lower than or do mee. I., protocably between 2 and 25.degree. C. The pH at which the thirties of tyles in the the temperature is carried out is mostly between 5.5 and 12, protocably solves or and m.

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in place the two <u>circles in the action</u> and the working up of the reaction mixture are mostly carried out in water. Optionally, the reaction mixture may also contain an organic solvent or a mixture or organic solvents, preferably loss than 30 vol. . Examples of organic solvents that can be used are alsohols with 1-7 parbon atoms, for instance a monoalcohol, in particular solvent 1 to other 1; a 3i 1, in particular solvent slyvel is a trible in

## 1.11111

AMI Dogramming

## Barr:

AMF1.3H.sub.L 0=mmploillin tribyumate

## 11.21....

### . . . . . .

### FW 15 respectively a strong energy as

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### 11.59:

Encymatics coupling of ZII am of FGA and ZII am of  $\frac{1-ABA}{1-ABA}$  at 5. degree. 1., till we any working eq.

A next are of five of the  $\frac{1-AiA}{2}$  and  $\frac{A}{2}$  to deform what suspended in  $\frac{1}{2}$  of the water and suspended in  $\frac{1}{2}$  of the water and suspended in  $\frac{1}{2}$  of the water and supper substituting encycle is the first of the supper substitution of the substitution of the water and supper 1. Wet encycle (substitution of water and supper 1. Wet encycle (substitution of water) and supper 1.

## 1 1 1 1 1 1

After I hours the pH had riven to hole, by beans of otherntrated aque us NH. subtantine pH was brought to how and after 1 minutes the reaction mixture was foltered through a S-2 glass filter; the residue was washed with 1'1 ml of water to degree. Co. This residue was a mixture of enzyme and FO formed purious the reaction.

## 1877:

Exceptibility of I.I nM of FGA and III nM of 6-AFA at 5.degree. C., followed by working up.

### DEFR:

A mixture of 43.9 g of 6-AFA and 30.6 g of PGA was suspended in 877 ml of water and cooled to 5.degree. C. The resulting suspension was added to 100 g of [wet] immobilized Pon-3 adylase from Recordati [Milan]. This enzyme is connercially available in a mixture of water and glycerol ([wet\_ennyme]); here was washed three times with 100 ml of water.

## 18114:

After 1 hours the pH haderisen to 6.0. By means of concentrated aqueous NH.sub.7 the pH was brought to 6.6 and after 0 minutes the reaction mixture was filtered through a 3-3 glass filter; the residue was washed with 100 ml of water 10.degree. C.1. This residue was a mixture of encyme and PS formed during the reaction.

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la Alguerias de percepcios <u>anglides in</u> tron a nixe de containing <u>angreplin</u> and description pentrole, carego <u>iz</u>alà compresion:

### 11.11.15

4. A process sooth Will to claim 1, wherein the mixture followins (-0) mol — st <u>othick</u> was pleated relative to the butal arount of <u>severa and ampionisin</u>.

### NIFR:

i. A process according to claim 1, wherein the mixture contains 8-8% mol  $_{\odot}$  =  $_{\odot}$ 

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II. A probles for recovering appointlin from a mixture containing appicition and  $\ell$ -which problem and  $\ell$ -AFAC origination

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In Agreement and rather than the main lip wherein in the <u>equiphance</u> anylate in asserting the pH in maintains by morth lies a said, in the arm heap and wherein that is turn for pH in any mplished by removing arminish.

# 11.1 11:

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chosining a risture containing  $\frac{anpivelien}{and}$  and  $\frac{a}{a}$ -amini penicillin that is prepared from the reaction mixture of an encymatic adulation reaction in which  $\frac{a}{a}$ -AFA is adulated using D-phenylglycineamide (PGA) or esters of  $\frac{a}{a}$ -phenylglycine, said mixture having an initial pH greater than T; and

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iedudica toe pH or gelia mixture and drystallicing fur <u>emplocitio</u>.

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ommanie il antigora a mosto de la Augusta de la mara calcinina a combineà. Il lina de la calcinia de la grando no la granda el mara calcinina a combineà. on pentration of any ating agent plus wheta. Hartan derivative of at least 400

### ABFL:

.beta.-Rabtam derivatives are synthesided by an engymatic reaction of the parent arine thoratela man with the torresponding advisting agent, the end section of the anything agent plus the contentration of thems. Flaman denoted by the contentration of the approximation of the section of the contentration of the contentrat

### 33F84

This invention relates to a process for the preparation of .beta.-lastam derivatives by ensymatry appliation of the parent aming .beta.-lattam with an acylating agent. The amino .beta.-lactam may be  $\frac{6-aminopenicillanic abid}{16-APA}$ , 7-aminodesacetomycephalosporamic abid (7-ADCA), Teaming dephalosporanio agid THACA; or Teaming-3-phloro-3-dephem-4-darhowylate and pro- anylating agent may be a designified of <u>Copperpig.yours</u> or jejenyar mygneny. ny time.

### 1.

Today, semisymthetic .betw.-lactams such as <u>Ampivillin,</u> Amexicillin, bisalor, Sephalemin, Sephadromil and Sephaloglysin are prepared in industry by shemical methods, for example by reacting an amino .beta.-lastam such as a-aminopeninillanio apid, usually having its carboxyl group protested, with an group by hydrolysis. It is important due to, for example, yield, that the aming .beta.-lastam, for example 6-AlA, is used in a pure, dry form, manno are alternation and the example of such as used in dispersion, the property of the property of their states. For example, Ampioilling the property of th r med vising somirions and organic solvents like mothylene chloride and 

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noise.

Shipparton properties of <u>Apportition</u> receiptive <u>s-AFA and a G-phonylghysine</u>

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of pupils and application Division. West Arman patent applicant to beyond . The problem of problem is a sum of the problem of the problem in the problem in the problem is a sum of the problem in the 337, 1<u>8</u>15.

ners.
The arm observable man such as <u>weaks</u> is something or involved the <u>community</u>

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In eq. (FM, income as ), it is not not be purposed and crystallized to obtain pure wealth of -Ai/A in the -Ai/A tare, the temperted periodillic nave seen the up, another process before the mylicularist step ...

### B. EB:

The pitential prawkarks of the known <u>endymetro</u> methods for production of Amplo, No., Amimodillin and Cephalemin none have yet been upscaled to industrial applicability are the high stats yield lesses and investments to the high state when the amino applications of the high states when the amino applications of an estimate when the amino applications of an estimate when the amino applications of an estimate when the amino applications of the estimate when the amino applications are the estimated when the estimated wh , to, and a, post file commission to the training special life contract saw that excess 1.1 The ara na na arrang ta ar remargni heta na kengalar ana baranen baranen baranen baran baran baran baran baran bar And while for his or the <u>France are very one typotally less than to mM , thus</u> nature the late of the formed <u>Arms to be not a quitously and the same and the same of the sam</u> Firtip. Also, a nisher yieldizh the e<u>bhyreti</u>n binnat billef <u>Arbigillia</u> es 19-20 1 34 19 4

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A process for  $\frac{\sin y \cos z}{z}$  synthesis of Ar. w. colling is described in Agric. Soci. Them. 44 for , but st seq., which process is performed in a reaction medium containing and z or time volume or more of degrap and and z or younge volume. or ther alternate. When he of the last mentioned alternals or 2.5 of Legg part. The level, the initial parter that it the starting materials, it lightless that materials, it lightless that may be be and the manufactor of the legger to be perfectly, then it is a legger to be as a legger to be a legge the-initial concentration of the starting materials, 0-.alpha.-(p-hydroxyphenyl) glycino mothyl cotor and  $\frac{\epsilon$ -aminopenicillanic acid, is 460 and 230 mM, respectively. It is stated in this paper that the addition of more than 100 mM of D-.alpha.-(p-hydroxyphenyl)glycine methyl ester and of more than 50 mM of  $\epsilon$ -aminopenicillanic acid markedly suppressed the ration of conversion of  $\hat{e}$ -aminopenicillanic acid into amoxicillin. The conclusion of this statement is that this publication teaches away for increasing the An Anteres in the arm of Angle and if the application and in the remarks a rise and

### H39F:

After the effective filing date of the application for a patent on this invention, namely Sep. 18-21, 1990, a poster was published at a MATO Workshop. The poster dealt with the preparation of pephalosporins and, according to this preser, working at low temperature had several positive effects on the The first term of the contraction of anylating agent used by this work was a second of the contraction of anylating agent used by this work was a second of the appraising only or grown betry, ested and there was no indicate no because you are the contractions of the Apprentiate in the anylating appli-

## BSFR:

It has now, surprisingly, been found that the yield in the enzymatic preparation of .beta.-lactam derivatives can be improved by carrying out the reaction at high concentrations of the adjusting agent.

Fig. the process of this invention, it is possible and Attractive to use a probability in the constituent of research and Attractive to use a probability in the constituent of research  $\frac{1}{2} \frac{1}{2} \frac{1$ porition to a prignant this is now apple, Approxiling Americal and Separation are thus minimized as poritionation equipment former used for tably type of <u>FAHA</u> is we can be used for is classically <u>Ampedilling</u> Americalling and Aphaleschic

## H. 11 H :

Advantage thely, the high yield are idinate this invention can be distanced And the land of the first term to be an arranged by the transfer of the second of the

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Annual navy, into inventor provided a provided for engination feature of the food and an inventor of the food and the following of the followi

### H 155:

In the appear, this growes is the appearance; in the translation of the property of the property of the control of the respect of the control of the respect of the control of the second of the control of the respect of the control of control of control of the control of the control of control of control of the control of the control of contr

### THER:

Examples of .Pota. - lactam derivatives that may be produced by the process of this invention are Amportillin, Amonicillin, Cefactor, Cephalexin, Cephadroxil.

The adviating agent may be a derivative of <u>D-ph-pylipyline</u> or D-p-nyin mythonylily line such as a lower alkyl methyl, ethyl, n-propyl or as propyl estate or an anise which is unsubstituted in the --TONE.sub.2 group. In an 3 to proper to the Berivative may be used in the type of a salt, for example, the HTD salt or the H.sub.. Susub.4 salt. The adviating agent may be added in an active form of the active form may be formed in situ.

### TEFR

The engages to be used in the process of this invention may be any <u>charged</u> paralyzing the reaction in question. Such <u>engages</u> have such above of more such as each of the sample, terms i pentallin aminase or pentallin abylase and plassified as E.C. Willill. A number of microbial companies of microbial companies, the engages are entered to the actionary, derived from the example forespector, familiarly, by place, in terminal and the familiar Mest German patent application having patent application. No. 11- flot,
Agnancoladium, Sephal spirom (Mest German patent application naving publication naving publication No. 3.0.1817, Kluyvera strophila Agr. Biol. Chem. 37 (1974), JTAT-18741 and Examples this soli West German patent application having publication No. 3.0.7817, Kluyvera strophila Agr. Biol. Chem. 37 (1974), JTAT-18741 and Examples this soli was terman patent application having publication No. 3.0.7817, Kluyvera strophila Agr. Biol. Chem. 37 (1974), JTAT-18741 and Examples this soli engage is commercially available. The engage also may be a second this soli engage to Estate the Examples of this constitution is in this constitution, reference to, interesting that to Hadde to Engage and Jahot, Jife & Don, to other patents of which this constitution is the second of the constitution o

1815:

in la pasterros for la sofre progression a respessión format d'example, el entrapper o como a live do for, Immatlicato n'appres incorpany any any any momento a. Immatlique format disa colo <u>angune</u> important praelly available from branchinger Mannheir Ro, H., Ferraky, under the grade name Encygel.

The solubility of the adulating agent such as the <u>C-phenylilycine</u> or The Physic Ryphenyl styring desirative will vary with the identity of the agency of the section <u>leps survives of the later of the later and the sale of the second of t</u> as in the pH value and the temperature if the solution. In some embodiments of the process in this invention, the initial reaction mixture is a slurry convisioning unities lived adylating agent and or .neta.-ladtum, which will dissolve partly to cully during the course of the reaction. The .neta.-ladtum times may praint that among the reading and, elst, the byth lysis prototic of the advision agent with an <u>lepton, the</u> and lepton with any or the region of the seasons. He has a slundy the teams, the team who

The amin: .reta.-lastam, for exemple 6-A/A or 0-A00A, used in the process of this invention may be obtained by  $\underline{encymatic}$  hydrolysis of the fermented penicillins or cephalosporins, (for example penicillin V, penicillin G or bephalosporin 0; br their ring enlarged analogues (for smample Y-DCA and 3-50A) or derivatives thereof followed by removal of the hydrolysis by-product, if desired (phenoxyacetic acid etc.). Advantageously, the crude solution can be used directly without further purification or dilution.

### : EFF:

Generally, the reaction temperature of the process of this invention may vary between about Alagmee. 2. and about 30.degree. 2., is especially between shout 10. Magree. 1. and about 30. degree. C. Temperatures in the range about .negree.=37.degree. 7. may be preferred for forvenient speration. The suitable pH value depends on the type and purity of entype. Using Escherichia coli encyme, the pH value is typically in the range from about 5.5 through ..., professibly in the Manne from about (.1 through about 7 preparation of Americalian, a pH value in the range from about 8.5 through la le ... is professed. There's of the pH value may be used. Suitable reaction times are in a several minutes to several nours, in particular from about 1 nous of an electronic for able engine on temprations may be from about I Tables In the Single and Tables and Tables and thing, she below .

## DEFR:

Using the process apporting to this invention, extraordinary high yields can re obtained. The high yields are obtained using the teachings of this invention and properly selecting the concentration of the adylating agent, the ratio between the confeneration of adylating agent and the starting amino .gega.-lamam, the pH rains and the <u>elignma</u>.

A second to a special as a splace activity to a llowing is used for during spray meets one of one of second that my highest per minute luminosis per violation of an interest per violation of a contract of the violation of Butter, pH ville, t. , of degree. . . .

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A solution of the RM <u>e-APA</u> and P-PHA in a contentration as indicated in table. The Sale sale is to the particle of the pa

## 1 E F B :

James am activities out Example 1, http://doi.org/ HADMA is used Instead of <u>pHADA</u>. This objects when the company is a Mighillesian in a stalley that the maximum well by a stalled at auspears of the other any automatical Halbard and Halbard and Abadia and Ab

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If the k-A+A and T is not let TA sulphate sulthare adjusted to a pH value as unitaries in rable S, and the <u>encyratic synthesis</u> is carried out at A1. degree, T, and TB states not the TB states TB states and TB solutions, in the TB states TB solutions.

## 113:

If so the with in -m + -ki A and -i + k A . Find at  $j \in V$  which k, k and  $k \in V$  is limited things from Espherichia following total produces k and promine the symmetric constants. temperatures as indigated in Taple 4, the maximal yields of <u>Ampirollon</u> intained are shown in Table 4.

## 1 201 2

This emangle was perpurped analaginaly with Emanple 1 using 1-83M instead if I-3  $\mu_{\rm e}$  . The magnitum yields on  ${\it Ample}_{
m e}$  . ${\it Lin}$  invarined are as stated in Table 5.

den Vijartiy pininga irom tempentati nipritniny foltration, extrastion int purpu aberale and cark into an aqueous phase resulting in a solution of tweight volume open V is hydrolysed by Semacylase.TM. (immobilized pen V acylase from Novo Mordisk A/S) at a pH value of 7.0. The phenoxyacetic acid is removed by excraction and to the resulting  $\underline{e-APA}$  (150 mM) solution, containing minor amounts of hiproducts from degraded pen V and 6-APA, is added 45 %ml soluble endyse from Escheribhia coli and D-EGA (to a final Concentration of TIME yH value is adjusted to %.4 and the reaction is allowed to rropena at ublandrow. To keeping the pH dalue constant.

### 1. Ell E :

Under those minditions a total of lib minole of <u>Amploil in 1960</u> is formed per liter of reaction volume.

Difference of impositived entropy is suspended ad 10 ml with water. The entropy solution was nixed with a solution of e-ALA and D-FOA to a total volume of 25 ml the resultion relations of notations of  $\frac{1}{2}$  ml the resultion relations of notations of  $\frac{1}{2}$  ml  $\frac{1}{2}$  and  $\frac{1}{2}$  ml  $\frac{1}{2}$  having the value of  $\frac{1}{2}$  and  $\frac{1}{2}$  ml  $\frac{1}{2}$  having the value of  $\frac{1}{2}$  and  $\frac{1}{2}$  must be solved as  $\frac{1}{2}$  must be solved at  $\frac{1}{2}$  must be suffered which of  $\frac{1}{2}$  is the  $\frac{1}{2}$  mass of the state of  $\frac{1}{2}$  must be  $\frac{1}{2}$  and  $\frac{1}{2}$  must be suffered to  $\frac{1}{2}$  must be  $\frac{1}{2}$  and  $\frac{1}{2}$  must be suffered which of  $\frac{1}{2}$  is the  $\frac{1}{2}$  must be suffered as  $\frac{1}{2}$  must be sufficient as  $\frac{1}{2}$  must be suffered as  $\frac{1}{2$ 

A mixture of 96% mg e-APA and 3018 mg HFGA in water is adjusted to pH & .2 at 16.degree. 7. and 16% U soluble penicillin 3 acylase from E. coli is added to a final volume of 10% out. The synthesis is allowed to proceed at constant temperature, using .8 givelbillians to seek the point to... Altri 10% in the top read .25 mixture 20% of the pilotop to seek the point to seek the pilotop to a yield the read to the seek the pilotop to a yield the read to the seek the pilotop to a yield to the seek the pilotop seek the pilotop to a yield

## 1833

If we are soluble peninclian  $\mathcal F$  anylase from  $\mathcal F$ , notices and its a minimum of  $\frac{1}{2}$  and HF  $\mathcal F$  and  $\mathcal F$  of the same final concentration, respectively in water tropp and the various of the control of the control

From the with 1% of  $\epsilon$ -ArA, will small HEVA, letwin solution generally in a applied for F. will, 14% of Ar windlin with a way provided after 8 hours, when the reaction, has been a completely and a first series.

The conditions is described in example to ising  $C=\pi M$  and  $AC=\pi M$  and  $AC=\pi M$ 

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regulated and the entered of the effect of Architecture after the effect
1816:
......
K-ABA is c-quintportivillant, avia, M-ALMA is M-aminidesa metinyisephalospiranto
avid, h-BBA is D-phenylgiydinanide, iFGM is h-phenylgiydin methyl ester, M-CMA
 is Thy henomy a set amododes a betomy pephalosporanio a ord, Tohota is
   Teghen, La retambut dewa retomy teghal hay trahib lagogi ama EPGA is
 lepenyar szypneny, asyminari le.
    a: :::
  <u> Polymanie rypinie rie – i <u>Aidie (1979).</u></u>
  <u>proprio exprinesio i Septialexia.</u>
  Burgario symiesis ti Artxidilim.
  <u>Encymatic</u> synthesis of Amomicillin.
   DEPU:
  Enzymatic synthesis of Amoxicillin.
   <u>Encymatle</u> synthesis of Amemicillin.
   Betentilh times in minungs: 4.1 Detal; 6.3 (T-ADDA); 6.1 (<u>K-AFA</u>); 9.1
      n-FGA', 19.4 Coghalomin', 13.9 (Arrivallin), 18 (D-FGM),
   ( EPV:
   Retention times in minutes: 2.5 (D-p-hydroxyphenylglycine*; 3.3 (HESA*; 5.4
      .6-ArA'; 13.0 'Amquicillin .
   : E::::::
     TABLE 6
     reaction time, my hours
     1. In the proper for the preparation of a theratelectam amide comprising
    enter the contract of the state of the contracting of a period in,
     Than in the same my reginal sportants and, Tham increpital sportants acid and having the first and and having the first and the sportants with an applicable of the sportants of
     of Lebrah life the liberalelation amide is amovicillin and the appliating about is 1-alpha. - p-hydroxy-phonyl alycine mothyl ester, the improvement
      is Delaipna. Expense of the control 
     amino im the restrict mixture prester than 400 mM and the <u>entype</u> is derived them a rinter transfer entype is derived them a rinter transfer selected in the structure trustation of Escherichia coli, Acetyles to a set currante. Manthophas contii, Eluyver, citrophila, or Bacillus
     per participation in a
      1115:
      w. Agr week association of state to a 2, wherein the aminochests. Hastar is
      <u>- - artinggen, og liggi – gårgi.</u> T-artingdes a est ångdephalles pårante lakti.
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europo (grae og gamen aged og Mearop en mol di enemgrape element wydatra.

## 11111:

. A process and sing to claim 1 in m, wherein the adylating agent is <u>legneny alvouse</u> or legeny accepy heny laly one or decreasives there. 1.

oner. M. Alger the Carteres design to train of each or all American the interaction and design the second section of the section of the second section of the section

in. A process actor bing to claim 1 or 1, wherein the connectivation is the aming .peta.-lagram in the reaction mixture when the enginetic reaction starts is in the range from about 51 to about 750 mM,

one. A process army into the claim laim laim, wherein the conventments of anylating agent, in the reaction numbure when the <u>provincies</u> reaction stable is granter that it in Ma

11. A pricess are raing to claim 10, wherein the mincentration of the as, lating agent in the reast is mixture when the edge aris reaction starts is greater than "".  $\pi M$ .

In. A process ancoming to blaim 1 or 2, wherein the amount of the adylating agent in the reaction mixture when the <u>enzymation</u> reaction starts is above the solubility of the agent in the reaction mixture.

us. A process according to claim 1 or 1, wherein the amount of the adylating agent in the starting reaction mixture is greater than half the amount of said agent which is soluble in the reaction mixture plus the arount of the arino beta.-lastam in the reastion mixture when the ensymmatic reaction starts.

33. A process according to claim 1 or 2, wherein the  $\frac{encyme}{e}$  used is classified as  $87^{-3}.6.1.11$ .

The  $A_{ij}$  is the second since i . This is a summarish the energy densities which ihymal, by your much that state the

38. A process according to claim 1 or 0, wherein an growns in reusable form is 4564

en. A promess and touch to state I may, wherein the <u>enument</u> meantion is Service of the Boundary of Carry